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Locally Administered Ocular Corticosteroids

Benefits and Risks

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Abstract

Corticosteroids, used prudently, are one of the most potent and effective modalities available in the treatment of ocular inflammation. However, they can produce a plethora of adverse ocular and systemic events. In order to optimise and target drug delivery, whilst minimising systemic adverse effects, a diverse range of local ophthalmic preparations and delivery techniques have been developed. Topical drops and ointments remain the primary methods for administration of ocular corticosteroids. However, ocular penetration of topical corticosteroid drops depends upon drug concentration, chemical formulation of corticosteroid, and composition of the vehicle, therefore, apparently small modifications in preparations can produce a more than 20-fold difference in intraocular drug concentration. Periocular injections of corticosteroids continue to have a useful, but limited, therapeutic role and longer acting, intraocular delayed-release devices are in early clinical studies. Although newer corticosteroids with lesser pressure elevating characteristics have been developed, corticosteroid-induced ocular hypertension and glaucoma continue to be significant risks of local and systemic administration. Posterior subcapsular cataract, observed following as little as 4 months topical corticosteroids use, is thought to be due to covalent binding of corticosteroid to lens protein with subsequent oxidation. Inappropriate use of topical corticosteroid in the presence of corneal infections also continues to be a cause of ocular morbidity. Other risks of locally administered ophthalmic corti-

costeroids include: tear-film instability, epithelial toxicity, crystalline keratopathy, decreased wound strength, orbital fat atrophy, ptosis, limitation of ocular movement, inadvertent intraocular injection, and reduction in endogenous cortisol. This extensive review assesses the therapeutic benefits of locally administered ocular corticosteroids in the context of the risks of adverse effects.

1. Local Ocular Administration of Corticosteroids

Systemic corticosteroids were introduced more widely into ophthalmic clinical practice in the 1950s as a major advance in the control of ocular inflammation.[1] However, within a few years, in addition to systemic adverse events, a number of ocular-specific glucocorticoid adverse effects, such as cataract and elevated intraocular pressure (IOP), had been reported.[2-6] In order to optimise ocular drug delivery, while minimising systemic adverse events, a diverse range of local drops, ointments, delayed-release topical vehicles, and intraocular, periocular and oral corticosteroid preparations have been developed over the last 50 years.[7] However, despite the continuing development of techniques and vehicles for local administration of corticosteroids, systemic and ocular adverse events continue to be identified with dermatological, inhaled and ocular corticosteroid preparations.[8-13] Complications of local ocular administration of corticosteroids are highlighted in table I.

Although nonsteroidal anti-inflammatory drugs (NSAIDs) have been shown to rival the therapeutic efficacy of corticosteroids in a number of ophthalmic conditions without the associated risk of elevated IOP, decreased wound strength or predisposition to infection,[14-16] topical corticosteroids remain an indispensable component of the ophthalmic therapeutic armamentarium. Although the clinical benefits and adverse events associated with such corticosteroid preparations have been well documented, their basic pharmacokinetics in the human eye have yet to be fully elucidated. Although an increasing amount of literature has addressed this point, particularly over the last 15 years,[7,17-28] much of the knowledge of these drugs has been gained by extrapolation of data obtained from rabbit models.[29-57]

Because of differences in anatomy and technical aspects of experimental studies, animal results can vary significantly from human data; these differences include 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.[46,58-60] It has also been demonstrated that the rabbit cornea becomes significantly less permeable with age, particularly for large hydrophilic compounds,[61] suggesting that direct extrapolation from data on young laboratory animals to the elderly human cornea is of limited utility. In general, measurements of steroid concentration in rabbit eyes[30,35,41,47-49,52,53] tend to be significantly higher than those recorded in humans.[17-22] However, because of the relatively limited data on human eyes, this review

Table I. Complications of local ocular administration of corticosteroids

Ocular surface epithelial toxicity
Delayed epithelial healing
Reduced wound strength
Keratocyte apoptosis
Corneal deposits
Exacerbation of microbial infection
Reactivation of herpes simplex keratitis
Crystalline keratopathy
Corticosteroid-induced ocular hypertension/glaucoma
Corticosteroid-induced posterior subcapsular cataract
Lid ptosis
Dilated pupil
Extraocular muscle imbalance
Orbital fat atrophy
Intraocular vascular occlusion/haemorrhage
Accidental intraocular penetration
Systemic absorption
Systemic glucocorticoid suppression

includes both animal and human data with the foregoing reservations.

In relation to systemic administration, local administration of ocular steroids theoretically enables smaller doses for equivalent or greater local steroid concentration, more target-specific drug application, and reduced systemic adverse events. The extent of the disparity between systemic and topical dose to achieve similar ocular concentrations is seldom fully appreciated. Indeed, in the rabbit model it has been shown that an intravenous dose equivalent to 5.0g in a 70kg human is required to produce aqueous humour concentrations comparable to those achieved after topical dexamethasone alcohol drops. A similar intravenous dose of prednisolone produced a peak aqueous concentration only 50% of that obtained by four drops of topical methylprednisolone 0.5%.[30] Similarly, intramuscular methylprednisolone in monkeys produced total ocular tissue concentrations which were less than 1% of those obtained by a similar dose given as a periocular injection.[62] In practice, maximal intraocular steroid concentration may actually represent as little as 0.05% of an intravenous dose.[60] Obviously, systemic corticosteroids continue to have an important role in ophthalmic practice, such as in the management of corneal graft rejection, severe uveitis and scleritis, but they act primarily by affecting the systemic limb of ocular disease. There may be superior local methods of producing significant intraocular concentrations of steroid.[63-65] However, a number of complications of corticosteroids, such as steroid-related glaucoma, subcapsular cataract and reactivation of herpes simplex, are common to both local and systemic corticosteroids.[6,13,66,67] Methods of local ocular corticosteroid delivery are highlighted in table II.

Table II. Route of ocular corticosteroid administration

Topical application
Drops: solutions and suspensions
Ointments and gels
Impregnated collagen shields
Impregnated contact lenses
Iontophoresis
Liposome preparations
Ocular/periocular injection techniques
Subconjunctival injection
Subtenons injection
Peribulbar/retrobulbar injection
Intravitreal injection
Slow-release anterior chamber devices
Slow-release intravitreal devices
Supratarsal injection
Intralesional injection
Systemic administration
Oral
Intramuscular
Intravenous
Subcutaneous

2. Topical Ophthalmic Drops and Ointments

Topical ophthalmic drop preparations remain the most common method of administering corticosteroids to the eye, and steroid reaches the aqueous humour within 5 to 30 minutes of application.[7,18-21] The majority of topical preparations are provided at a concentration of 0.1 to 1.0%. Unsurprisingly, increased steroid concentration in topical preparations generally results in higher intraocular concentrations,[41,42] but for prednisolone acetate, a frequently used topical steroid, the optimum dose-response effect in experimental keratitis occurs at a 1% concentration.[48] Increasing the ocular contact time by preparing topical steroids in a microsuspension,[53] gel or viscous formulation,[23,68] can double the corneal and aqueous humour concentrations of steroid, compared with the same drug applied as a solution.[23,41,68] Other apparently minor changes in formulation, such as the addition of the preservative benzalkonium, can significantly alter the pharmacokinetics of topical steroids.[41,68]

Most of a topically applied corticosteroid penetrates the eye via the cornea.[68] The greatest barrier to this intraocular penetration is the lipid-rich corneal epithelium, which retards the ingress of polar, hydrophilic derivatives such as prednisolone phosphate.[37,40,44] However, this is much less of a barrier to lipophilic derivatives such as the alcohol and acetate forms of dexamethasone and pred-

nisolone.[43,44,48,54,69] The absence of corneal epithelium following surgery or trauma can produce significantly greater penetration of topical steroids, and higher corneal concentrations of steroid may also occur in the presence of intraocular inflammation.[37] However, the concomitant application of an antibacterial drop within 60 seconds of steroid application can reduce the bioavailability of the applied steroid by almost 70%.[51] The additive effects of increased concentration, lipophilic derivation, and the increased contact time afforded by a microsuspension have been demonstrated in humans. Indeed, comparing single topical application, a single drop of prednisolone acetate 1.0% microsuspension produces intraocular steroid concentrations 20-fold those of prednisolone phosphate 0.5% solution[19,21] and almost 100-fold those of betamethasone phosphate 0.1% solution.[20] In contrast, when dexamethasone, prednisolone and fluorometholone are all formulated at an equivalent 0.1% concentration in an identical vehicle, the rabbit aqueous humour concentrations of these steroids are almost identical.[47] In a human study of an aqueous drop containing dexamethasone-cyclodextrin-polymer co-complexes, it was demonstrated that this formulation improves the aqueous humour penetration of dexamethasone by approximately 2.6 times compared with the commercially available (dexamethasone alcohol 0.1%) solution, by enhancing both solubility and permeability through the cornea.[23]

It is essential, when comparing data in respect to penetration of corticosteroids into aqueous humour, to recall that the systemic anti-inflammatory effect of both betamethasone and dexamethasone is five to seven times that of prednisolone.[70,71] The local anti-inflammatory potency of ocular steroids has yet to be fully investigated, and while early work suggested that prednisolone acetate 1% had the greatest anti-inflammatory effect in experimental keratitis,[45] subsequent studies demonstrated that fluorometholone acetate in a 1% formulation was equally efficacious in the same model.[54]

The data on intraocular penetration of corticosteroids are often contradictory, and the reasons for this are multiple. Drug formulation, as discussed, can alter the bioavailability significantly. The method of delivery, whether drop, ointment, injection (intravitreal, subconjunctival, peribulbar, retrobulbar) and even route of injection (via skin or conjunctiva) will alter the pharmacokinetics and thus the intraocular concentration significantly. The data on comparative penetration of ocular and systemic corticosteroids to the human eye are presented in table III. Importantly, rabbit-based research has shown seemingly unrelated variables to alter absorption. Sieg et al. [46] demonstrated a large increase in time to peak concentration, in anaesthetised compared with unanaesthetised animals. They also noted, when comparing penetration in erect and recumbent rabbits, that the difference in time to peak concentration was small, but this was overshadowed by an over two-fold increase in magnitude of the peak concentration in recumbent animals.[46] Measurement of intraocular concentration is also subject to variation depending on the assay used. High performance liquid chromatography (HPLC), gas chromatography with mass spectrometry (GCMS) and radioimmunoassay are all widely used techniques, but do have slight differences in sensitivity and specificity. For example, radioimmunoassay, while very sensitive, measures a surrogate for the drug (i.e. a radiolabel which may be attached to the original drug or a metabolite thereof) and can therefore be prone to confounding measurement errors.[22]

It has been established that fluorometholone, which has a reduced ability to elevate IOP and penetrates into human aqueous humour less than prednisolone or dexamethasone,[7] undergoes local ocular metabolism in the cornea.[75] Local ocular metabolism of the relatively new, potent, topical anti-inflammatory corticosteroid rimexolone 1.0% may also explain the reduced likelihood of raised IOP with this steroid.[76] Loteprednol, a 'soft' steroid, belongs to a unique class of corticosteroids with a metabolically labile 17β-chloromethyl ester, which is designed to be hydrolysed to a metabolically inactive carboxylic acid moiety.[57] Interestingly, concentrations of loteprednol and ratio of

Table III. Comparative penetration of ocular and systemic corticosteroids in the human eye

Drug	Route	No. of subjects	Dose[a]	Peak concentration (μg/L)			Time to peak (min)	Reference
				aqueous	vitreous (subretinal)	serum		
Dexamethasone disodium phosphate	Subconjunctival injection	50	2.5mg	858	72.5	32.4	150-180	24
Dexamethasone disodium phosphate	Peribulbar	50	5.0mg		(82.2)		180	25
Dexamethasone disodium phosphate	Subconjunctival injection	49	2.5mg		(359)		147	25
Dexamethasone	Oral	49	7.5mg		(12.3)		304	25
Dexamethasone-cyclodextrin	Drops	47	0.32%	140			150	23
Dexamethasone alcohol	Drops	31	0.1%	62			150	23
Prednisolone sodium phosphate	Drops	93	0.5%	25.6			90-240	19
Dexamethasone alcohol	Drops	64	1.0%	31.0			91-120	18
Prednisolone acetate	Drops	58	1.0%	1130			30-45	17
Prednisolone acetate	Drops	66	1.0%	669.9			120	21
Fluorometholone alcohol	Drops	22	0.1%	5.1			31-60	21
Clobetasone butyrate	Ointment	10	0.1%	0.1			780[b]	28
Betamethasone	Ointment	13	0.1%	20.3			780[b]	28
Betamethasone sodium phosphate	Drops	66	0.1%	7.7			91-120	20
Betamethasone	Drops	45	0.1%			0.5	30	72
Methylprednisolone	Oral	16	8mg			66.58	132	73
Hemisuccinate methylprednisolone	Intravenous	50	500mg		332-456	9480	150-360[c]	74

a Percentage concentration is given for medication administered as one drop.

b Measurements were made from 12.5 to 18.5 hours after administration and may have missed the peak aqueous concentration.

c Time to peak in vitreous. Peak in serum is instantaneous because of intravenous bolus.

metabolites to unchanged drug are greatest in the cornea, suggesting this is the primary site of deactivation.

It has not been established which minimum concentration of steroid is optimum for minor ocular inflammatory conditions such as postoperative uveitis, and although concentrations of 670 μg/L of prednisolone have been recorded in human aqueous humour,[21] perhaps lower concentrations[19] may be sufficient to suppress inflammation and minimise adverse events.[77] For comparison, following topical application, peak timolol concentrations of 2500 μg/L have been recorded in rabbit aqueous humour, yet β-adrenoceptor blockade can be obtained with as little as 9 μg/L.[78]

Preparation of prednisolone acetate as a gel provides a more prolonged release[79] and higher peak aqueous concentration than an equivalent topical solution.[52] However, some viscous agents and ointments may actually produce lower peak ocular concentrations of steroid when compared with drops.[40,79] Johansen et al.[56] have demonstrated that prednisolone acetate in the high-viscous, water-soluble polymer carbomer (carbomer 0.5%) produced higher corneal, conjunctival and aqueous humour concentrations of prednisolone than those obtained by an aqueous suspension. However, because of 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.[40] Ointments do have some advantages in children because of their prolonged release. Ointments are also particularly useful for overnight treatment as an adjunct to daytime drops in certain inflammatory conditions.

3. Periocular and Intraocular Injections

It is generally believed that most topical and subconjunctival steroid enters the eye via the tear film and thence the cornea; thus radiolabelled hydrocortisone produces only 2.5% of the anticipated aqueous humour concentration when corneal penetration was prevented, compared with topical application with free access to the cornea.[80] Experimentally, repeated subconjunctival injections of prednisolone (50mg) have been shown to be inferior to hourly topical prednisolone acetate 1% drops (6.5mg) in reducing the inflammatory response in keratitis.[50]

Early analytical techniques suggested that subconjunctivally injected steroid entered the eye via the sclera.[33] The sclera is readily permeable to even relatively large molecules such as albumin;[81] therefore high concentrations of corticosteroid can be detected in the sclera directly underlying a subconjunctival injection site.[33] Recent research has also highlighted that the isolated sclera is up to five times more permeable than the cornea to hydrocortisone, suggesting there may be an aqueous pore pathway in the sclera compared with the transcellular pathway in the cornea.[55] However, most subconjunctival steroid appears to enter the eye by diffusing through the puncture site in the conjunctiva into the tear film, and then via the cornea into the intraocular milieu.[29,32] In this context it is not unexpected that subtenons injections of methylprednisolone in monkeys produced significant anterior segment steroid concentrations (approximately 25 μg/L) but could produce peak vitreous concentrations of only 2 μg/L.[82] In contrast, retrobulbar methylprednisolone in the same model produced much higher posterior uveal/retinal concentrations and significant vitreous concentrations which persisted for up to 9 days.[62] These discrepancies might be partly explained by the lack of post-equatorial diffusion of drug following subconjunctival and subtenons injections.[60] It is notable that total ocular steroid levels may actually be lower following peribulbar injections in inflamed than non-inflamed eyes. This is in contrast to topical steroid drops, which exhibit enhanced corneal penetration in inflamed eyes.[60]

Bodker et al.[83] investigated subconjunctival and retrobulbar injection of dexamethasone in a rabbit model and, interestingly, dexamethasone levels were similar in aqueous, vitreous and retina at 1 and 4 hours for both groups. Importantly, with the exception of retinal concentrations in the subconjunctival group, the contralateral eye provided almost identical concentrations to the ipsilateral eye at 4 hours, suggesting that dexamethasone absorption and delivery was mainly haematogenous in this rabbit study. An absorption model for prednisolone following subconjunctival injection in rabbits confirmed that only 0.2% of the applied dose is absorbed into the vitreous and that 98% is absorbed into the systemic circulation with a half-life of 38 minutes.[84]

In an elegant study, Weijtens et al.[24] assessed the relative penetration of dexamethasone disodium phosphate into 50 human eyes after subconjunctival injection, and compared findings with their prior studies of the oral and peribulbar routes. In a series of eyes undergoing pars plana vitrectomy, extremely high mean aqueous humour dexamethasone concentrations (858 μg/L) and high vitreous concentrations (72.5 μg/L) were obtained 2.5 to 3.0 hours after subconjunctival injection. The gradient between the aqueous and vitreous humour suggested that a significant route of penetration into the vitreous was, as previously noted, via the cornea and aqueous, in addition to the trans-scleral and haematogenous routes. The relative vitreous concentration of dexamethasone following subconjunctival injection was 3 times and 12 times greater, respectively, than after peribulbar and oral administration. However, the subconjunctival injection was still associated with significant systemic absorption with a mean serum concentration of 32.4 μg/L at 30 minutes.[24]

In a subsequent study, Weijtens et al.[25] assessed intraocular penetration of dexamethasone in 148 eyes with rhegmatogenous retinal detachment. In this prospective study, subjects received either subconjunctival dexamethasone disodium phos-

phate (2.5mg), peribulbar dexamethasone disodium phosphate (5.0mg), or an oral dose of 7.5mg dexamethasone. Dexamethasone disodium phosphate is hydrolysed to dexamethasone by esterases which are present in the aqueous, cornea, tears and possibly other ocular tissues.[85] The dexamethasone concentration in subretinal fluid, aspirated intraoperatively, was measured by radioimmunoassay with estimated maximum concentrations of 359, 82.2 and 12.3 μg/L, respectively. The concentration of dexamethasone in subretinal fluid was significantly higher after subconjunctival injection than after administration by peribulbar and oral routes in this study,[25] and achieved concentrations much higher than had been reported in the vitreous humour (72.5 μg/L) after the same subconjunctival dose in a previous study.[24] Aqueous humour dexamethasone concentration after subconjunctival injection of dexamethasone disodium phosphate (2.5mg) has been demonstrated to be much higher (peak of 858 μg/L)[24] than after a single 50μl drop (0.05mg) topical application of dexamethasone alcohol 0.1% (peak of 31 μg/L),[18] though comparative data following multiple drop application are not available in humans.

The inherent risks of periocular injection of steroid, (section 10) and the availability of alternative, equivalent or superior methods of application, mean that the role of periocular injection is limited to a few situations. Such situations include providing immediate postoperative anti-inflammatory cover at the end of intraocular surgical procedures and less common scenarios such as the short-term use of orbital floor corticosteroids in non-necrotising scleritis.[63] The role of retrobulbar steroid in the treatment of persistent macular oedema remains unresolved.[86] In a recent series of 57 eyes with uveitis-associated chronic cystoid macular oedema, Rojas et al.[87] noted that trans-septal injection of corticosteroids did not provide superior resolution to that of oral corticosteroids and NSAIDs, or a combination of trans-septal and oral corticosteroids, although overall 79% of eyes gained two or more lines of vision after a minimum of 6 months follow-up.

While intravitreal antibacterials have become a standard treatment for endophthalmitis, the use of intravitreal corticosteroids 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.[88] 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 μg/L may persist for up to 4 days.[89]

4. Alternative Administration Techniques

Waltman and Kaufmann[90] 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.[91] established that hydrophilic contact lenses, presoaked in 1% prednisolone phosphate, produced an aqueous humour peak concentration that was three to four times 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 although not widely used and despite some limitations, have been shown to be a viable alternative to topical drops in certain patients.[92] To minimise the need for repeated instillation of topical corticosteroids, Baeyens et al.[93] have described a soluble ocular insert device which releases dexamethasone and gentamicin concomitantly for 10 hours and thereafter gentamicin alone for 50 hours. 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.[94]

The development of dissolving collagen shields has rekindled interest in such methods of delivering ophthalmic drugs, and shields presoaked in tobramycin have been well tolerated by patients[95] and have been shown to produce higher aqueous

and corneal concentrations of antibiotics than subconjunctival injections.[96] Collagen shields have also been suggested as the optimum vehicle for poorly soluble drugs such as cyclosporin.[97] It has been demonstrated that collagen shields presoaked in dexamethasone alcohol produce superior intraocular concentrations of dexamethasone to those produced by hourly drops over the first 4 hours, and that a 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.[98] Collagen shields appear to provide increased compliance, better 24-hour control, and higher ocular drug concentrations than comparable methods of administration, coupled with good patient tolerance. However, they have yet to gain wide acceptance by clinicians and it has already been highlighted that certain antibacterial and corticosteroid combinations in collagen shields may provoke adverse corneal reactions.[99] Bucolo et al.[100] used corneal shields derived from hyaluronic acid to deliver methylprednisolone to rabbit eyes and identified zero-order kinetics with almost constant levels in tear film for 48 hours, compared with undetectable levels of methylprednisolone 3 hours after a topical drop.

Using a novel application technique, during laser *in situ* keratomileusis (LASIK) surgery of the cornea, Peters et al.[101] divided 210 eyes into two groups: group A received the standard topical postoperative treatment, and group B received topical prednisolone sodium phosphate 1.0% solution on the under surface of the surgical corneal flap (i.e. essentially intrastromal), in addition to the standardised postoperative medication. The incidence of nonspecific diffuse intralamellar keratitis (DLK) in group A was 17.1% and in group B was 6.7%. Therefore, eyes receiving the single drop of intrastromal steroid had significantly less post-LASIK inflammation in terms of DLK ($p < 0.01$), although inflammation *per se* is usually minimal following LASIK surgery.

The incorporation of drugs into liposomes has demonstrated up to 10-fold improvement in the intraocular penetration of hydrophilic drugs following topical application;[102] however, possibly because a number of the commonly used ophthalmic corticosteroids are already lipophilic, there has, as yet, been little use of liposome delivery for corticosteroids. Transcorneal and trans-scleral iontophoresis of polar drugs, which normally penetrate these structures poorly, remains largely experimental.[103]

Intraocular slow release devices continue to be developed for specific indications in the eye. Zhou et al.[104] have developed a prototype multiple-drug delivery implant for proliferative vitreoretinopathy, composed of poly(dl-lactide-co-glycolide) [PLGA] to deliver 5-fluorouridine, triamcinolone and recombinant tissue plasminogen in three cylindrical segments. This implant can be delivered into the vitreous by a 20-gauge syringe needle and has delayed release of up to 1 month. To achieve prolonged release, Jaffe et al.[105] used a nonbiodegradable drug delivery device to deliver fluocinolone acetonide into the vitreous cavity, with vitreous concentrations of 0.10 to 0.21 mg/ml in a rabbit model. Theoretically, such devices could be used in cases of chronic posterior uveitis with a 2.0mg device providing slow release for 2.7 years and a 15.0mg device lasting 18.6 years. Interestingly, with this device no corticosteroid was detectable in the aqueous humour.

Chang et al.[106] evaluated the efficacy of an intraocular biodegradable polymer dexamethasone drug delivery system (DEX DDS) in treating postoperative inflammation after cataract surgery. Patients receiving DEX DDS showed a significant reduction in postoperative inflammation ($p = 0.002$), and required rescue treatment with topical corticosteroids less frequently than the control patients (80 *vs* 7%, $p < 0.001$). These results have been verified in a randomised, masked and partially controlled trial by Tan et al.,[107] in which intraocular anterior chamber placement of a single 60µg DEX DDS was found to be a well tolerated and effective treatment for reducing intraocular inflammation after cataract surgery. Interestingly, there was no statistical difference in efficacy between the intraocular device and 0.1% dexamethasone eyedrops

in reducing intraocular inflammation, as measured by clinical methods, while the DEX DDS was superior to eyedrops in reducing aqueous flare as objectively assessed with the laser flare meter. No significant difference in endothelial cell loss was noted between DEX DDS-treated eyes and dexamethasone eyedrop-treated eyes, for up to 1 year after surgery, and the only local reaction to the insert was clinically insignificant peripheral anterior synechiae at the site, in 6 of the 29 patients.[107]

5. Corticosteroid-Induced Glaucoma and Ocular Hypertension

The use of topical ophthalmic corticosteroids can elevate IOP in some individuals. This is known as corticosteroid-induced ocular hypertension.[108-114] Corticosteroid-induced glaucoma occurs when this IOP elevation persists and results in glaucomatous visual field loss and characteristic optic nerve changes. Corticosteroid-induced ocular hypertension usually occurs within a few weeks of treatment with potent corticosteroids, or within months with the weaker steroids.[115] Rarely, it may have a more acute presentation occurring within hours or days of administration of potent topical corticosteroids.[116] The population can be divided into two general groups: a minority called 'steroid responders' who exhibit this response in a mild or severe form, and a majority in whom treatment with corticosteroids does not result in elevation of IOP.[109,117] In the general population, 4 to 6% are likely to be 'high responders', with elevations of IOP greater than 15mm Hg, and approximately one-third will be 'moderate responders', with increases in IOP between 6 and 15mm Hg after daily corticosteroid treatment for 4 to 6 weeks. Two-thirds of the general population will have an IOP rise of less than 6mm Hg and are considered to be 'nonresponders'.[118]

Certain groups are considered to be at higher risk of being steroid responders. Those with known primary open angle glaucoma or a family history of the disease are more likely to be steroid responders.[119,120] In individuals with glaucoma, approximately 46% will have an IOP rise greater than 15mm Hg and an equal number will have an increase in IOP between 6 and 15mm Hg from baseline.[121] Patients with high myopia,[122] diabetes mellitus,[123] or connective tissue disease[124] (especially rheumatoid arthritis) seem to have a similar predisposition to corticosteroid-induced ocular hypertension. Interestingly, steroid responders may be at higher risk for developing glaucoma over time.[125,126] The effect of topical corticosteroids on IOP in children is variable. Some studies suggest that children have a lower incidence of positive steroid response than adults.[127] However, IOP elevation has been precipitated in children after strabismus surgery.[128] In one randomised clinical trial in a Chinese population,[129] children exhibited a greater and more rapid ocular hypertensive response to topical dexamethasone, reaching their peak IOP after only 8 days of topical dexamethasone 0.1%.

Currently it is impossible, on an individual basis, to predict which patient will be a steroid responder, other than those with aforementioned risk factors; therefore, judicious use of topical corticosteroids is essential. This can be accomplished by avoiding topical corticosteroids if a safer drug will suffice, using one of the corticosteroids that is known to result in less IOP elevation, and monitoring IOP closely for the duration of corticosteroid therapy.

In general, the ability of a particular corticosteroid to induce elevation of IOP is proportional to several factors: its anti-inflammatory potency, the dosage of the drug, and duration of treatment. Therefore, prednisolone, dexamethasone and betamethasone, which are potent corticosteroids, tend to produce corticosteroid-induced ocular hypertension more often than less potent corticosteroids. Interestingly, the formulation may also influence the ocular hypertensive property of the agent. For example, dexamethasone acetate 0.1% has a greater anti-inflammatory effect but the same effect on IOP elevation as the equivalent dose of dexamethasone sodium phosphate.[130]

In a series of 53 patients with uveitis, the use of a longer-acting, posterior subtenons, depot cortico-

steroid (triamcinolone acetonide), was associated with a significant rise in IOP in 36% of eyes, and glaucoma drainage surgery was required in more than 10%.[131] In contrast, in a retrospective study of patients who had been exposed to topical or systemic corticosteroids, and had not exhibited steroid responsiveness, an analysis of 202 consecutive posterior subtenons injections of either methylprednisolone or triamcinolone demonstrated no significant elevation of IOP.[132] Kalina[133] excised depot steroid from seven human eyes that had received subconjunctival triamcinolone. The mean IOP was reduced from 37 to 16mm Hg and active steroid was identified in deposits up to 13 months old. Intravitreal triamcinolone, used in the treatment of age-related macular degeneration, has also been associated with uncontrolled glaucoma and steroid cataract.[134] Subconjunctival injection of depot methylprednisolone has also been associated with a necrotising conjunctival ulcer in one report.[135] Therefore, on the basis of these studies, caution should be taken in the use of injectable long-acting depot steroids in the treatment of ocular disease in patients with unknown steroid responsiveness.

A group of corticosteroids have been developed which have useful anti-inflammatory properties but a lower propensity to elevate IOP.[136] Drugs in this group include medrysone, fluorometholone, rimexolone, clobetasone and loteprednol. Medrysone, primarily used in the treatment of external eye disease, since it has limited corneal penetration, has little or no associated IOP elevation.[137,138] Fluorometholone 0.25% results in substantially less elevation in IOP than dexamethasone 0.1%,[113,139-142] although significant pressure rises have still been observed.[139,142,143] Quantification of its anti-inflammatory effect indicates that fluorometholone 0.1% is an effective, but weaker, anti-inflammatory agent compared with prednisolone and dexamethasone.[138] Interestingly, commercially available fluorometholone preparations penetrate into the human aqueous humour less than commercially available prednisolone or dexamethasone preparations.[7,18-21]

Rimexolone is a water-insoluble anti-inflammatory corticosteroid. In a double-masked, randomised, single eye crossover trial in patients who were known corticosteroid responders, rimexolone demonstrated that it has limited potential to elevate IOP.[136] Patients treated with rimexolone had lower IOP than patients treated with dexamethasone sodium phosphate and prednisolone acetate by 4.2 and 5.8mm Hg, respectively. Furthermore, the time to the onset of the increase in IOP was longer (5.2 weeks) with rimexolone application than with dexamethasone sodium phosphate (3.0 weeks) and prednisolone acetate (2.5 weeks). Nevertheless, it has been suggested that topical rimexolone 1% is clinically and statistically equivalent to topical prednisolone acetate 1% in controlling ocular inflammation.[144]

Clobetasone butyrate 0.1% has been shown to produce less elevation in IOP, but also less anti-inflammatory action.[77,138] Several double-blind, multicentre clinical trials have investigated the anti-inflammatory properties of clobetasone butyrate. Most[77,145] have shown that the anti-inflammatory properties of clobetasone butyrate are similar to those of betamethasone phosphate and prednisolone phosphate. Known steroid responders treated with clobetasone in one eye and prednisolone in the other eye had a significantly lower rise in IOP with topical clobetasone (approximately 7.0mm Hg).[145] However, Dunne and Travers[146] concluded that although clobetasone butyrate had less effect on IOP elevation, overall it also had less anti-inflammatory effect in eyes with anterior uveitis.

As previously noted, loteprednol etabonate is a novel site-active corticosteroid synthesised through structural modifications of prednisolone-related compounds so that it will undergo a predictable transformation to an inactive metabolite. Randomised, double-masked, crossover studies[147-149] have demonstrated that loteprednol etabonate 0.5% has less effect on IOP elevation than prednisolone acetate. In one study, only 3 of 117 patients had IOP elevation >10mm Hg during the 2 weeks of application.[150] Another study showed that loteprednol

increased IOP by 23.5% while prednisolone acetate resulted in a 49% increase in IOP from baseline.[148] However, in this study loteprednol etabonate was also shown to be less effective in controlling the signs and symptoms of anterior uveitis than prednisolone acetate. Other studies suggest that loteprednol can result in a clinically meaningful reduction in the signs and symptoms of postoperative inflammation following cataract surgery.[151] Double-masked studies evaluating the elevation of IOP with long-term (>28 days) use of loteprednol etabonate noted that loteprednol increased IOP by >10mm Hg in fewer than 1% of 1648 patients compared with 6.7% for prednisolone acetate.[152]

Most evidence suggests that the cause of corticosteroid-induced hypertension is a reduction in outflow of aqueous fluid through the trabecular meshwork in the anterior chamber of the eye in susceptible individuals.[120] Corticosteroids have been shown to bind to specific receptors[118] in the trabecular meshwork cells and have been linked to the following trabecular meshwork effects: alterations of extracellular matrix material,[153-156] induction of myocilin, induction of myocilin-related proteins[157] and decreased phagocytosis.[158-160] Myocilin is part of a group of stress proteins that can be induced by subjecting the trabecular cells to various insults.[161] This protein was initially found to be increased in experimental glucocorticoid-induced glaucoma. The gene coding for myocilin (MYOC), initially known as trabecular meshwork-induced glucocorticoid response protein (TIGR), has been identified at the GLC1A locus of chromosome 1.[162-165] This gene has been identified in association with juvenile open-angle glaucoma. It is postulated that the myocilin gene induces a protein, myocilin, which is secreted by the trabecular meshwork cells. This activation of myocilin may alter the expression of trabecular meshwork genes, leading to changes in extracellular matrix. Accumulation of abnormal extracellular material beneath the inner wall of the endothelium of Schlemms canal could, in turn, increase the outflow resistance to aqueous flow and cause elevated IOP.[154]

A second hypothesis is that a mutation in the myocilin protein may prevent it from performing its physiological intracellular functions.[66,162] Mutations in the protein have been found in between 3.5 and 5% of persons with open angle glaucoma.[166] Although even higher rates have been identified in juvenile open angle glaucoma, mutations are present in 1.6% of normal individuals.[167]

IOP elevation usually normalises within 1 to 4 weeks after discontinuation of the corticosteroid. Rarely, the elevated IOP may persist despite cessation of treatment. This is more likely if there is a family history of glaucoma,[115] or with long-term corticosteroid use.[168] If the IOP remains elevated despite discontinuation of the corticosteroid, the patient may require long-term treatment with an ocular antihypertensive medication. Interestingly, Halpern et al.[169] performed a pharmacoeconomic analysis of the use of a corticosteroid with low IOP-elevating potential (rimexolone) to treat ocular inflammatory conditions. If used in preference to corticosteroids with greater IOP-elevating potential, the authors calculated that $US10 million (1995 values) would be saved annually in US healthcare.

6. Corticosteroid-Induced Subcapsular Cataract

The original association between systemic corticosteroids and posterior subcapsular cataract (PSC) was identified by Black et al.[3] in 39% of 44 patients with rheumatoid arthritis who had been treated with corticosteroids. Since then a large number of studies have confirmed the association of PSC and systemic corticosteroids in diseases such as asthma, nephrotic syndrome, renal transplant and systemic lupus erythematosus.[6] Corticosteroid-induced cataracts have been associated with topical dermatological preparations and inhaled corticosteroids.[8-10] The first report of PSC associated with topical ocular corticosteroids appeared in 1963.[2] A number of subsequent publications have confirmed this association.[6]

The prevailing mechanism by which corticosteroid causes PSC is thought to be that of covalent

binding of the steroid to lens protein, resulting in oxidation of the protein structure; however, an alternative mechanism such as a glucocorticoid-mediated receptor effect is also possible.[170] To test the former hypothesis, Dickerson et al.[170] studied dexamethasone, aldosterone and progesterone using an *in vitro* lens culture technique. They noted that non-glucocorticoid steroids bound to lens protein as well as, or better than, corticosteroids, although binding was blocked by pretreatment of lens protein by aspirin (acetylsalicylic acid). Although the authors concluded that corticosteroid-induced cataract must be due to a mechanism other than covalent binding of steroid to lens protein, only corticosteroids produced significant reduction in glutathione levels, a known feature of other forms of cataract.[170] Bovine lens epithelium contains a 28kD protein that can bind progesterone and possibly other steroids with high affinity; the protein appears to be microsomal and may mediate steroid effects that contribute to cataract formation.[171] A significant association has been noted between reticulation of human lens epithelium and use of topical steroids prior to cataract surgery, possibly confirming that steroid-induced cataract may be due to altered anterior lens epithelial cell function.[172] Topical and systemic tocopherol (vitamin E) has been used to protect against steroid-induced cataract in animal models.[173,174]

The relative risk of developing cataract after topical corticosteroid use has yet to be fully elucidated but is related to length of administration and intraocular penetration of steroid. Donshik et al.[175] followed 86 patients with keratoconus receiving long-term, potent, topical corticosteroids after corneal transplantation, and at a mean of 18 months, 28 had developed PSC which was related to total topical dose and duration of administration. However, even corticosteroids noted to have low IOP-elevating propensity and poor intraocular penetration,[21] such as fluorometholone, have been reported to cause cataract after a continuous 4-month application period.[176]

7. Corticosteroids and Ocular Infection

The use of corticosteroids in combination with antimicrobial drugs in the treatment of infectious corneal disease remains controversial.[177] In animal models of experimental bacterial keratitis, treatment with topical antibacterials to which the organism is sensitive, in combination with a corticosteroid, may not adversely affect treatment of the infection, and may actually reduce the severity of inflammation.[178-180] However, there are significant risks of using corticosteroids in the presence of frank or latent infection. Corticosteroids are absolutely contraindicated in fungal keratitis and relatively contraindicated in acanthamoeba keratitis.[177]

In general practice, topical corticosteroid treatment of herpes simplex virus (HSV) keratitis is strongly contraindicated, since it has been known for more than quarter of a century that misapplication of corticosteroids in herpetic eye disease can result in significant complications, in terms of the severity and morbidity of the keratitis.[181] Kaufman et al.[67] noted that the response of HSV to corticosteroids is determined by the genome of the virus, some strains behaving virulently in the presence of corticosteroids, and some not. However, severity or worsening of the disease with corticosteroid was not correlated with establishment of trigeminal ganglionic virus colonisation, suggesting establishment of HSV latency is not affected by corticosteroid use.[67] Ocular herpes simplex reactivation by corticosteroids has been experimentally demonstrated in dogs and rabbits after multiple or even single doses of systemic corticosteroid.[182,183] In a prospective randomised, double-masked, placebo-controlled study of HSV stromal keratitis, resolution of stromal inflammation was quicker in the group treated with combination topical corticosteroid and antiviral therapy than in the group treated with an antiviral alone. However, no differences between the groups were identified at 6 months after starting treatment.[184] In relation to other viral keratitides, the antiadenoviral activity of topical cidofovir has been shown to be significantly reversed by concomitant topical corticoste-

roid application, in terms of adenovirus eye titres, adenovirus-positive eyes and prolonged adenovirus shedding.[185]

Use of corticosteroids in microbial keratitis may mask the presentation and delay appropriate management.[186] A multivariate analysis of a series of 227 cases of microbial keratitis identified significant association between the use of topical corticosteroids and *Streptococcus pneumoniae* infections, and corneal exposure and prior use of topical corticosteroids were associated with prolonged hospital stay.[187] Use of topical corticosteroids has also been associated as a risk factor for severe keratitis in a subtropical climate.[188] Miedziak et al.[189] identified prior use of topical corticosteroids as a major risk factor in a large study of microbial keratitis (n = 162) that ultimately required treatment by penetrating keratoplasty. An association, though not necessarily a causal association, with the use of topical ocular corticosteroids has also been identified in patients who have microbial keratitis that progresses to endophthalmitis with the same pathogen.[190]

In a deliberate attempt to reduce inflammation in cases of endophthalmitis, intravitreal corticosteroids have been combined with intravitreal antibacterials. However, Meredith et al.[191] demonstrated in an aphakic rabbit model with severe *Staphylococcus aureus* endophthalmitis, that neither systemic nor intravitreal dexamethasone improved the final outcome; indeed, intravitreal dexamethasone on day 1 increased the severity of the inflammation. In contrast, other authors have noted a benefit of intraocular corticosteroids, with improved preservation of the electroretinogram response following administration of intravitreal dexamethasone at 36 hours in a rabbit model.[192] These data suggest some caution in regard to the use of intravitreal corticosteroids in the treatment of endophthalmitis. Two recent human studies confirm that benefits of intravitreal corticosteroids may be limited. Das et al.,[193] in a study of 63 eyes with exogenous endophthalmitis, compared vitrectomy with coadministration of intravitreal antibacterials, with or without intravitreal dexamethasone. Although the inflammatory score was reduced in the dexamethasone group at 1 and 4 weeks, inflammation was similar at 12 weeks and there was no independent influence on visual outcome. In a retrospective study of 57 eyes, treated by vitrectomy and intravitreal antibacterials, or vitrectomy, intravitreal antibacterials and intravitreal dexamethasone, Shah et al.[194] identified, by multivariate logistic analysis, that the use of intravitreal corticosteroids actually reduced the probability of gaining a three-line improvement in visual acuity by a factor of 3.5.[194]

In an assessment of postcataract surgery antibacterial plus corticosteroid regimens, van Endt et al.[195] found that fluorometholone plus gentamicin produced a significantly lower bacterial colony count on days 6 to 8 after surgery than dexamethasone plus neomycin plus polymixin B, without any difference in intraocular inflammation.[195] Patients after cataract surgery are generally treated with topical corticosteroids for less than 4 weeks; however, after corneal transplant surgery, patients may apply topical corticosteroids for several months or even years. This long-term exposure to corticosteroids is associated with a rare, rather peculiar, low-grade corneal infection, which presents with feathery crystal-like corneal infiltrates termed crystalline keratopathy.[196] This condition has also been identified in a case following trabeculectomy for glaucoma and administration of low-dose topical corticosteroids.[197]

8. Adverse Effects on Surgical Wound Healing

Topical ophthalmic corticosteroids are commonly used in the postoperative setting to reduce inflammation. Along with this anti-inflammatory effect, however, there is a plethora of concurrent local effects. In animal studies, corticosteroids have been shown to retard corneal epithelial regeneration and inhibit stromal healing[36,59,198] and even cause superficial epithelial necrosis.[199] Endothelial repair may also be delayed by corticosteroids, in a definite dose-response relationship.[200] In cats subjected to either clear corneal or limbal

surgical incisions, corticosteroid treatment inhibited wound healing in both. Limbal incisions healed faster than their respective clear corneal counterparts, but at 28 days, regardless of treatment modality or site of incision, all wounds were almost completely healed.[201] However, in contrast, in human eyes after photo-refractive keratectomy (PRK), Rask et al.[202] reported that topical corticosteroid treatment did not impair corneal epithelial healing.

Keratocytes play an important role in maintaining corneal structural integrity, producing collagen and other components of the extracellular matrix. Altered keratocyte function may play a role in decreased corneal regeneration and strength. Experimental PRK ablations in rabbits caused an instant reduction in corneal keratocyte number in treated eyes, and at 12 months an acellular zone of 30 to 50μm was maintained in the corticosteroid-treated eyes,[203] suggesting steroid-induced keratocyte inhibition. Bourcier et al.[204] identified the glucocorticoid receptor on human keratocytes *in vitro*, but found that dexamethasone increased keratocyte proliferation by up to three times normal levels. However, they also demonstrated that dexamethasone induced keratocyte apoptosis and necrosis, even in low corticosteroid concentrations. Additionally, the percentage of viable cells, after treatment with corticosteroid, was decreased.[204] This paradoxical effect of increased cellular proliferation has been observed in a study on corticosteroid use after trabeculectomy surgery. A significant increase in filtering bleb encapsulation resulted after intra-tenons injections of 0.15ml of 24 mg/ml (3.6mg) dexamethasone over the trabeculectomy site. The authors postulate that the corticosteroid may have promoted, rather than inhibited, fibroblastic growth.[205]

Topical corticosteroids, even at a relatively low dose, have been shown to inhibit corneal wound strength in rabbits and humans.[36,59,206] Sugar et al.[59] demonstrated a significant reduction of rabbit corneal wound strength when treated with dexamethasone 0.1%. In rabbits this effect can be reduced if corticosteroids are used in conjunction with growth factors such as epidermal growth factor[207] or insulin.[208] Recent human studies link topical nerve growth factor application with increased corneal healing of neurotrophic ulcers.[206,209] Whether nerve growth factor or other growth factors, in conjunction with topical corticosteroids, can take advantage of the beneficial anti-inflammatory effect of corticosteroids, while minimising their ability to delay wound healing, remains to be seen.

Topical ophthalmic corticosteroids have been found to be absorbed systemically in sufficient quantity to inhibit wound healing in the untreated contralateral eye in animal models.[36,59,210] This is less likely in humans because of massive differences in dose and bodyweight. Interestingly, topical NSAID medications have not demonstrated any inhibition of corneal wound healing.[16,36] Indeed, a study by McCarey et al.[210] examined rabbit eyes after 8mm linear corneal wounds, treated with either prednisolone acetate 1%, diclofenac sodium 0.1% or flurbiprofen sodium 0.03%. Corticosteroid treatment caused weaker corneal wounds than in control eyes or NSAID-treated eyes, and the NSAID-treated eyes had stronger wounds than the corticosteroid-treated or control eyes.[210] Similarly, in cats, NSAID treatment did not inhibit healing of either corneal or limbal incisions.[211] Better corneal wound healing is not the only advantage NSAIDs have over corticosteroids; anterior chamber fluorophotometry has demonstrated ketorolac to be as effective as dexamethasone in re-establishing the blood-aqueous barrier after cataract surgery.[211] Thus NSAIDs remain an attractive alternative to corticosteroids in appropriate ocular surgery cases.[16]

With the advent of laser ablative refractive surgery, corticosteroids have been used in an attempt to minimise inflammation and scarring and to increase postoperative acuity and patient satisfaction. Studies of the effect of corticosteroid treatment in these eyes has highlighted a number of adverse events, such as pupillary mydriasis,[212] transient hyperopic shift[213] and raised IOP, while demonstrating no permanent beneficial effect on corneal haze or visual performance.[213,214] Clearly

their use in this setting is of questionable benefit.[215]

Debate continues in regard to the appropriate timing and use of corticosteroids in ocular alkali wounds, where collagenases and proteases may cause corneoscleral melt, which theoretically might be exacerbated by concurrent topical corticosteroid application. Evidence for delayed epithelial and endothelial healing exists;[216,217] however, corticosteroid treatment may protect the epithelial basement membrane.[216] Davis et al.,[218] in a retrospective study of 30 alkali burn eyes, demonstrated that intensive treatment with topical corticosteroids and ascorbic acid (vitamin C) had no significant association with corneoscleral melt. In rabbit experiments, alkali endothelial damage treated with dexamethasone exhibited slowed endothelial healing, but treatment also deterred the secondary endothelial breakdown evident in the control (nonsteroid-treated) corneas, indicating a possible therapeutic role.[217]

In summary, there is strong evidence in relation to animal models and compromised eyes for delayed corneal wound healing associated with topical corticosteroid administration; however, there is less evidence for clinically significant adverse effects secondary to this delayed healing in healthy eyes.

9. Systemic Absorption of Ocular Corticosteroids

The conjunctiva is thin and vascular, and facilitates rapid diffusion of oxygen and metabolites to and from adjacent structures, including the tear film. The lacrimal drainage system ports tears and solutes to the highly vascular and excellent absorptive medium, the nasal mucosa. In combination, these two routes provide potential access of topical ocular corticosteroids into the systemic circulation. In rabbit studies, despite the small volume of corticosteroid administered, topical drop application of corticosteroid produces significant liver, urine and plasma concentrations[68] and by 30 minutes almost a third of the applied steroid is distributed systemically,[31] with <5% being recoverable from the eye.[31,37] Because of this significant systemic dissemination of steroid, topical application inhibits corneal wound healing in both the treated and the untreated contralateral eye in rabbits.[59]

The hypothalamic-pituitary-adrenal axis is responsible for glucocorticoid regulation and has a sensitive negative feedback loop, decreasing corticotropin (ACTH) production in response to circulating corticosteroids. The effect of maintaining artificially high concentrations of circulating corticosteroids is widespread and includes the inhibition of endogenous cortisol production in the adrenal gland. After eight drops of prednisolone acetate 1.0% per day (4mg of prednisolone per day), both small dogs[219] and large dogs (up to 41kg)[220] have exhibited adrenal suppression, although the adrenal axis is more readily suppressed in dogs than in humans.[219,220] Spiess et al.[221] detected low serum concentrations of dexamethasone in horses after an 8-day regimen of unilateral dexamethasone 0.1% eye ointment, which then decreased to below detectable limits (0.06 μg/L) by 24 hours after cessation.

In humans, significant adrenal axis suppression has been reported after less than a week of topical dermatological corticosteroid use,[222] and in a study by Allenby et al.,[223] topical clobetasol propionate produced adrenal suppression in 25 of 39 patients treated in an appropriate manner for their respective skin diseases. The systemic absorption of topically applied ocular drugs such as β-adrenoceptor antagonists is well established;[12] however, the potential systemic effects of topical ocular corticosteroids are less clearly defined. While Burch et al.[224] observed a 50% decrease in endogenous corticosteroid production in male volunteers given hourly dexamethasone 0.1% drops (0.75mg dexamethasone per day) for 6 days, Krupin et al.[225] demonstrated a reduction in endogenous plasma cortisol but no adrenal axis suppression following eight drops of dexamethasone 0.1% per day for 6 weeks. Postoperative cataract patients given hourly dexamethasone 0.1% for 3 days exhibited a statistically significant reduction in plasma cortisol, but this remained within the physiological range.[226]

Both betamethasone 0.1% and loteprednol etabonate have been demonstrated to produce no significant drop in plasma cortisol with normal use. The former drug was detected in plasma to a lesser extent using a 0.05% formulation, while maintaining clinical efficacy, whereas the latter drug was undetectable in plasma altogether.[72,152]

It seems reasonable, therefore, to suggest that the possibility of adrenal suppression should be considered when ophthalmologists use intensive topical corticosteroids such as prednisolone acetate 1.0% and dexamethasone 0.1%. Notably, corticosteroid absorbed via the ocular or nasal mucous membranes does not undergo first-pass metabolism by the portal system. Therefore, intensive dosing such as hourly by day application, although totalling an empirical dose of only 6 to 8mg of prednisolone, or 0.6 to 0.8mg of dexamethasone, may produce an inherently greater corticosteroid effect than the equivalent orally administered dose. Special consideration should therefore be made when prescribing for infants and children, as the dose/weight ratio would place them at greater potential risk of adrenal suppression.

10. Miscellaneous Complications of Local Ocular Corticosteroids

A number of uncommon complications have been identified following administration of topical corticosteroids, including the previously noted infectious crystalline keratopathy,[227] corneal calcification associated with steroid phosphate preparations,[228,229] and tear film instability.[230] Periocular injection of corticosteroid has been associated with orbital rim fat atrophy[231] and limitation of ocular motility.[232] Intralesional injection of lid abnormalities such as chalazion[233] and capillary haemangioma[234] has been associated with ophthalmic artery occlusion and ipsilateral microembolisation and infarction of retinal and choroidal vasculature. In recent years mild ptosis, possibly related to the myopathic effect of topical corticosteroid preparations on Mullers muscle, has been identified in postrefractive surgery cases.[235] Indeed, in a study of 825 eyes after excimer laser refractive surgery, Loewenstein et al.[236] noted that 3.5% of eyes demonstrated a significant rise in IOP and 0.4% exhibited a ptosis. Prior studies on rhesus monkeys identified a 'steroid-induced' mydriasis and ptosis;[237] however, the investigators noted that pure dexamethasone in saline did not cause these effects and concluded that the mydriasis and ptosis were in fact caused by a direct myopathic effect of the vehicle rather than the corticosteroid.

The adverse events associated with systemic corticosteroids are well known to ophthalmologists; therefore, local administration is often seen as a logical method of producing maximum local effect while minimising such adverse events.[63] However, as previously discussed, local injection of corticosteroid has limited application, and specific local adverse effects are associated with these methods of administration. In a prospective, double-masked study of 246 patients undergoing cataract surgery,[238] it was noted that subconjunctival betamethasone resulted in a significant reduction in day 1 inflammation, and a reduced need for additional topical corticosteroids, while no eyes developed steroid-induced glaucoma. In contrast, a blinded, crossover study of 60 patients showed no benefit of subconjunctival corticosteroid in uncomplicated cataract surgery.[239]

Local injection of corticosteroids has other obvious inherent risks, such as bulbar perforation, choroidal injection, central retinal artery occlusion, and extraocular muscle imbalance, in addition to persistently raised IOP.[130,232,240] Gopal et al.[241] have reported on a series of five eyes in which accidental injection of intraocular steroid required subsequent vitrectomy.

11. Conclusion

Although more data on local application of ophthalmic corticosteroids in humans are becoming increasingly available, data derived from animal models is still heavily relied on. Fortunately, although some of the animal data are conflicting, recent studies suggest the general trends appear to be similar in humans. Interestingly, both animal and human data confirm the marked differences in

pharmacokinetic behaviour illustrated by identical concentrations of the same corticosteroid, in different topical formulations, such that generic equivalence cannot be assumed between preparations merely on the basis of equivalent corticosteroid content. Topical and local application of corticosteroids are preferable to systemic administration wherever possible; however, the limitations of, and alternatives to, subconjunctival and periocular injection should be carefully considered, as should the possibility of adrenal suppression following intensive ophthalmic corticosteroid drops in children and small adults. Almost 50 years after complications of topical ocular corticosteroids were first reported, a number of preparations and techniques have been developed to maximise anti-inflammatory effectiveness and yet minimise local ocular and systemic adverse events. Unfortunately, corticosteroid-induced glaucoma and cataract remain real risks in susceptible individuals, and the indiscriminate use of topical corticosteroids in ocular infections still carries significant ocular morbidity.

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