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Research Article

STEROIDS IN OPHTHALMOLOGY

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A R T I C L E I N F O

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A B S T R A C T

Corticosteroids, used cautiously, are one of the most potent and effective modalities of treatmentavailable for ocular inflammation, but their use is not without potential complications. Topical, subconjunctival, and sub-tenon application of corticosteroids are preferable to systemic administration in anterior segment diseases depending on the severity and level of inflammation. Systemic steroids are indicated in severe sight threatening diseases. The most common complicactions associated with long term steroid use are cataract and raised intraocular pressure. To prevent the ocular complications of steroid therapy, routine screening for cataracts, which occur most commonly as a sequela of continuous systemic steroid use, may be performed by slit-lamp examinations. Glaucoma is more often associated with topical ocular or periocular steroids than with systemic steroids; recommended screening includes a baseline intraocular pressure measurement, then routine pressure measurements are taken on subsequent follow-ups. Ocular rebound inflammation may develop secondary to rapid tapering or abrupt discontinuation of topical ocular steroid use and is best prevented with gradual tapering. Opportunistic infections of the eye include bacterial, viral, and fungal infections and are most often associated with the use of topical ocular steroids. Ophthalmologic evaluation is indicated promptly if patients treated with ocular steroids develop ocular discharge, pain, photophobia, or redness. In this review article we have highlighted the different topical steroids along with their use, side-effects and complications, periocular injections and intraocular injections along their steps of administration.

INTRODUCTION

Steroids in Ophthalmology

"Steroid" is a chemical name for any substance that has a characteristic chemical structure consisting of multiple chemical rings of connected atoms. It contains four cycloalkane rings

3 rings : cyclohexane
1 ring : cyclopentane

Corticosteroids are very effective for treating inflammation and immune -related ocular diseases[1]. Corticosteroid therapy has been applied in oculardisease from the moment it became generally available.[2] Corticosteroids, since their initial use in the 1950s, can be administered topically, regionally, or systemically.[3] Apart from their effect in reducing wound scarring, and suppression of inflammation, corticosteroids had little effect on the cause of inflammatory reactions. Therefore corticosteroids primarily control acute disease and are completely ineffective in the removal of structural damage caused by old or long standing inflammation.[1]

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Topical and systemic ocular corticosteroids on prolonged use can cause side effects, such as increased IOP, cataract formation. Regional administration has the advantage of minimizing systemic adverse effects, while maximizing drug delivery to the target tissue.[4]

Sources[5]

Zona Fasciculata (Adrenal cortex): They produce glucocorticoids.

e.g Cortisol , corticosterone, adrenal androgens and estrogens

ZONA GLOMERULOSA: They produce mineralocorticoids i.e aldosterone.

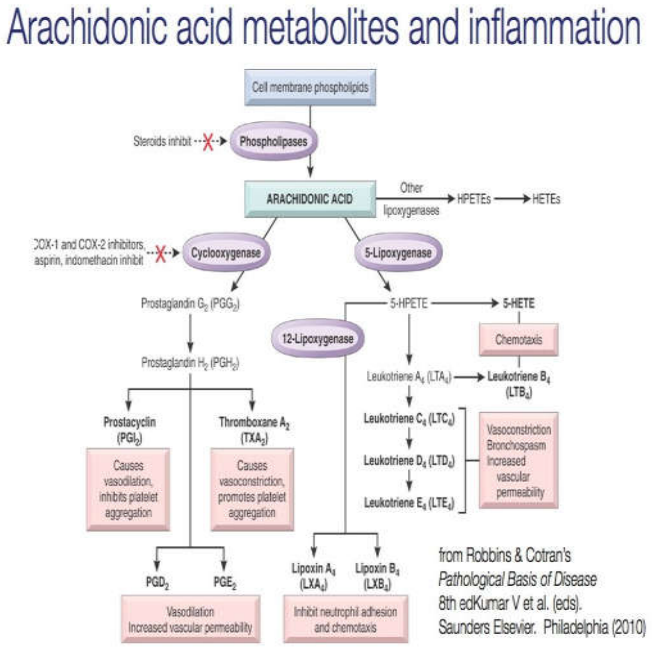
HPA Axis Suppression

Topical steroids used for ocular pathologies cause suppression of the HPA axis[6,7]. When exogenous, supraphysiological corticosteroid levels are administered, cortisol production is reduced by the adrenalglands (leading to adrenal atrophy), causing systemic effects that can lead to confusion, hyponatreamia, and life-threatening hypotension in the event of a trauma, surgery, or illness, known as an 'adrenal crisis.

So tapering is required i.e continuing the therapy for several days in reduced dose.

Basic steroidal activities towards inflammation

They act by suppressing the formation of arachidonic acid and other inflammatory mediators by the induction of phospholipase A2 inhibitory proteins, called lipocortins. Lysosomal membranes are stabilized and the production of lymphokines and prostaglandins is decreased which are the inflammatory mediators.



Commonly Used Topical Ophthalmic Formulations[8]

Corticosteroid	Derivative	Formulation	Concentration
Prednisolone	Acetate	suspension	0.5% or 1%
Prednisolone	Sodium phosphate	solution	0.5% or 1%
Dexamethasone	Alcohol	Suspension	0.1
Dexamethasone	Sodium phosphate	Solution Ointment	0.1 0.05
Flourometholone	Alcohol	Ointment Suspension	0.1 0.1
Flourometholone	Acetate	Suspension Suspension	0.25 0.1
Loteprednol	Etabonate	suspension	0.2% or 0.5%

Others include
Betamethasone ointment 0.1%
Clobetasone butyrate 0.1%
Rimexolone
Difluprednate

Routes of delivery

1. Topical – A) eye drops
   B) eye ointments
2. Periocular Injections –
   A)Sub conjunctival
   B)Sub tenon – anterior and posterior
   C)Retroseptal(orbital)
   D)retrobulbar
3. Intra Vitreal – injections
4. Systemic –A) Oral
   B)Parenteral – IV.IM

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 within15-30 minutes.[9]

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 abarrier to lipophilic derivatives such as the alcohol andacetate forms of dexamethasone and prednisolone.[9]

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 asdexamethasone phosphate results in only 25% less overall absorption of steroid than a single drop of the same steroid.[9]

Bioavailability of Topical Steroids

The ideal steroid should be biphasic i.e solubility in both the lipid (hydrophobic) layers of the epithelium and endothelium and the aqueous (hydrophilic) media of the stroma.

The acetate and alcohol derivatives more lipophilic i.e fat soluble whereas sodium phosphate and hydrochloride are more hydrophilic i.e water soluble. So, in intact epithelium, penetration of acetate is greater while in absence of epithelium penetration of phosphate greater.

Indications of topical steroids

Eyelids

1. Allergic blepharitis
2. Contact dermatitis
3. Herpes zoster dermatoblepharitis
4. Chemical burns
5. Intralesional Chalazion

Conjunctiva

1. Allergic conjunctivitis
2. Vernal conjunctivitis
3. Herpes zoster conjunctivitis
4. Chemical burns

Cornea

1. Herpes zoster keratitis
2. Disciform keratitis
3. Marginal corneal infiltrates
4. Superficial punctate keratitis
5. Chemical burns
6. Acne rosacea keratitis
7. Interstitial keratitis

Uvea

Anterior uveitis

Sclera

1. Scleritis
2. Episcleritis

Retina

Retinal vasculitis

Optic nerve

Optic neuritis
Temporal arteritis
(arteretic anterior ischaemic optic neuropathy)

Globe

Endophthalmitis
(except fungal endopthalmitis)
Hemorrhagic glaucoma

Orbit

Pseudotumor
Graves' ophthalmopathy

Extraocular muscles

Ocular myasthenia gravis

Post operative

Post SICS
Post Trabeculectomy

Periocular injections

Periocular injections can be performed using different injection techniques: into the subconjunctival space, into the sub-Tenon's space, into the orbital floor alongside the globe—usually inferiorly-via a transcutaneous or transconjunctival injection, or into the retrobulbar space[10]. Furthermore, regional corticosteroids injections often are a useful adjunct to systemic treatment for uveitis, when there is persistent or refractory macular edema[11]. The use of regional corticosteroids for the treatment of macular edema (ME) or active intraocular inflammation in uveitis is well established and widespread[12]. Sub-Tenon's injections can be given repeatedly; typically the effect on active inflammation is observed within days to weeks and improvement in visual acuity or macular edema occurs within weeks to months[12-14].

Blood – ocular barrier limiting diffusion is the main disadvantage.

Subconjunctival Inj– absorption occurs directly across the sclera.

Indications of Subconjunctival inj.–

1. Resistent anterior uveitis
2. Intermediate uveitis
3. Posterior uveitis,
4. CME (mainly unilateral) especially in patients contraindicated to systemic steroids and also who are non-compliant.
5. Patients where systemic steroids are contraindicated.

Sub Tenon (Anterior and Posterior) – suspensions are used for better absorption depot steroids used are

a. Inj methylprednisolone acetate
b. Inj triamcinolone acetonide

Peak action 4 weeks

Indications

Chronic intermediate or posterior uveitis

Procedure

1. Posterior subtenon injections were performed in the superotemporal quadrant according to the Nozik technique.
2. After topical anesthesia by tetracaine dropsand insertion of the lid speculum, the patient is instructed to look up and nasally.
3. A cottonswab soaked in tetracaine was applied over the conjunctiva at the site of injection.
4. The 25gauge tuberculin syringe is inserted bevelup against the sclera and advanced through the conjunctiva and Tenon's capsule using a side-to-side movement to ensure that thesclera was not engaged.
5. The needle is advanced along the sclera posteriorly and slowly with a side-to-side sweeping motion until the hub of the needle is reached and then the bevel end id rotated downwards.
6. Then, an injection of 1 ml 20 mg/mltriamcinolone was given. The eyelid speculum was removed.

The rate of IOP riseafter Anterior Subtenon Triamcinolone Acetonide (ASTT) injection is lower than Posterior Subtenon Triamcinolone Acetonide (PSTT) injection [15,16]

Retroseptal (Orbital) Injections[17]

Indications

1. Grave's disease
2. Orbital myositis

Intravitreal Injections

In the late 1970s, Machemer and McCuen established the safety of intravitreal triamcinolone acetonide (TA) and studied its effect on intraocular proliferation.[18,19] Intravitreal injection has the advantage of delivering thedrug more directly to the target tissue. However, a tradeoffis increased risk of complications that arise from injection directly into the eye.

By the late 1990s, there was increased clinical studyof intravitreal TA as a treatment for conditions including refractory macular edema and choroidal neovascularization[20-22]

Advantages

1. More targeted delivery
2. Controlled and consistent
3. Immediate achievement of therapeutic concentration
4. By passes BLOOD OCULAR barrier
5. Reduced systemic toxicity
6. Compliance eliminated

Indications

1. Treatment of diabetic retinopathy,
2. Cystoid macular oedema (CMO) associated with
3. uveitis, or Irvine Gass Syndrome
4. Birdshot retinochoroidopathy.
5. Exudativeage related macular degeneration (AMD).
6. Central retinal and Branch retinal vein occlusion
7. Neovascular Glaucoma
8. Ischaemic ophthalmopathy
9. Choroidal neovascularisation in ocular histoplasmosis.
10. Radiation induced macular odema
11. Exudative retinopathies

12. Eales Disease
13. Hypotony

Types and Formulations[24]

Triamcinolone acetonide – It is a minimally water-soluble suspension and acts essentially as a depotof sustained-release crystals when injected into the vitreous cavity. This leads to a longer half-life comparedto more water-soluble forms such as dexamethasone. It is available in single-dose vials at a concentration of 40mg/ml.

Intravitreal triamcinolone acetonide(IVTA), a suspension, is typically effective for about 3 months in a non-vitrectomized eye, so repeated injections may be necessary to maintain the treatment effect.

Dexamethasone – very short half life – 3-4 hours, hence, specific slow-release device has been made.

Ozurdex – A bioerodable, extended-release dexamethasone implant has received US FDA approval for the treatment of macular edema associated with retinal vein occlusion and noninfectious posterior segment uveitis. The device contains 700 µg of dexamethasone in a solid, bioerodable polymer.

Retisart - A non-bioerodable, extended-release fluocinolone acetonide implantable device which must be sutured to the sclera in an operating room, has received US FDA approval for the treatment of noninfectious posterior segment uveitis. The implant contains 0.59 mg of FA and was designed to deliver the drug for up to 1,000 days.

Mechanism of Intravitreal steroids

They stabilizes the blood–retinal barrier. It may also downregulatethe production of VEGF, which has been shownto be a vascular permeability factor that may be released by ischemic retina in diabetes mellitus. Inhibition of prostaglandins, which are known vascular permeability factors, may be an additional mechanism for reductionof macular edema[35-36]

Steps of Adminitration

1. Antiseptic measures are maintained.
2. Topical-anesthetic soaked cottontip is placed on the conjunctiva for approximately 1minute, then inject the local anesthetic toballoon the conjunctiva, using the cotton tipto disperse the anesthetic.
3. Caliper is used to measure 4 mm fromthe limbus (in a phakic eye) or 3.5 mm fromthe limbus in a pseudophakic or aphakiceye.
4. The steroidis pushed through to the tip ofthe needle to 0.1 cc total, and using a sterile cotton tip to stabilize the eye, inject 0.1 cc of steroid into the vitreous cavity while observing the needle tip. The needle is removed and a sterile cotton tip is placed over the needle entry site for several seconds.
5. A drop of topical broad spectrum antibiotic solution over the injection site.
6. The retina is observed for perfusion of the central retinal artery.
7. IOP is checked 30 minutes post procedure

Complications

1. Endophthalmitis
2. Pseudoendophthalmitis
3. Retinal detachment
4. Cataract progression
5. IOP rise
6. Vitreous haemorrhage
7. Central SerousChorioretinopathy
8. Central Retinal Artery Occlusion

Systemic steroids

Systemic steroids should be considered in patients with bilateral involvement, severe uveitis, lack of response or contraindications to periocular steroids.

The most widely used systemic steroids for uveitis are oral prednisolone and intravenous methylprednisone.

Suggested guidelines for the use of prednisone for chronic ocular inflammation :

Initial dose	1 mg/kg/day
Maximum adult oral dose	60–80 mg/day
Maintenance dose (adult)	10 mg per day
Tapering schedule	Over 40 mg/day, decrease by 10 mg/day every 1–2 weeks
	40–20 mg/day, decrease by 5 mg/day every 1–2 weeks
	20–10 mg/day, decrease by 2.5 mg/day every 1–2 weeks
	10–0 mg/day, decrease by 1–2.5 mg/day every 1–4 weeks
Supplemental treatment	Calcium 1,500 mg daily
	Vitamin D 800 IU daily
Monitor blood pressure, weight, glucose every 3 months	
Lipids (cholesterol and triglycerides) annually	

(Jabs DA, Rosenbaum JT, Foster CS, et al. Guidelines for the use of immunosuppressive drugs in patients with ocular inflammatory disorders: recommendations of an expert panel. Am Journal of Ophthalmology 2000;130:492-513)

Methyl Prednisolone Pulse

It is indicated in

1. Optic neuritis
2. Severe corneal graft rejection
3. Severe sight threatening posterior uveitis
4. Sympathetic ophthalmitis
5. VKH
6. Traumatic optic neuropathy Malignant exophthalmos

Dosing schedule-1gm IV (administered over a period of atleast 30 mins) for 3 days followed by oral prednisone in tapering doses.

Systemic Side Effects

1. Adrenal insufficiency
2. Delay in wound healing
3. Cushing's syndrome
4. Peptic ulceration
5. Osteoporosis
6. Hypertension
7. Muscle weakness or atrophy
8. Inhibition of growth
9. Diabetes
10. Activation of infection
11. Delay in wound healing

Contraindications

Generally contraindicated in:

1. Peptic ulcer
2. Osteoporosis(an increased risk of fracture)
3. psychoses

Ocular Side Effects

1. Posterior subcapsular cataracts
2. Ocular hypertension or glaucoma

3. Secondary ocular infection
4. Retardation of corneal epithelial healing
5. Keratitis
6. Corneal thinning or melting
7. Scleral thinning
8. Uveitis
9. Mydriasis
10. Ptosis
11. Transient ocular discomfort

Cataract

There is occurrence of Posterior subcapsular cataract with all routes High incidence is found in long term systemic therapy than the topical therapy.

Ocular hypertension or glaucoma[25]

Steroid induced glaucoma is a form of secondary open-angle glaucoma. There is reversible elevation of pressure with repeated use of topical steroids.

Mechanisms

1. Corticosteroids stabilizes lysosomal membranes and thus inhibit the release of hydrolases. Glycosaminoglycans present in the trabecular meshwork cannot depolymerize; they retain water in the extracellular space which leads to narrowing of the trabecular openings.
2. They suppress the phagocytic activity of endothelial cells of trabecular meshwork leading to collection of deberies in trabecular meshwork
3. They inhibit the formation of PGE and PGF leading to decrease in aqueous outflow facility.

All these mechanisms leads to obstruction of aqueous outflow leading to increase in iop.

Other side effects

Retardation of corneal epithelial healing due to its effect on effect on collagen synthesis and fibroblastic activity

Corticosteroid induce uveitis may also occur.

CONCLUSION

Ocular corticosteroids are widely used to control inflammation in different ocular conditions. Topical, subconjunctival, and sub-tenon application of corticosteroids are preferable to systemic administration in anterior segment diseases depending on the severity and level of inflammation. Systemic steroids are reserved for sight threatening disorders. The Royal College of Ophthalmologists in its Ophthalmic Service Guidance for Primary Care 2013 recommends: Slit lamp examination is required for any patient who requires prescription of topical steroids and in any patient who has a history of contact lens wear.

Intravitreal steroid injection appears to be an effective option for the treatment of macular edema secondary to various etiologies. An increasing number of ophthalmologists use intravitreal steroids for the treatment of various posterior segment disorders, especially when traditional therapeutic methods have failed. Novel agents including preservative-free and sustained-release intravitreal implants such as Ozurdex are currently approved for ocular use and are being further evaluated for the treatment of RVO, DME, uveitis, and AMD. Due to a potential for greater potency, dexamethasone and fluocinolone acetonide are being evaluated alone or in combination with anti-VEGFs as promising options in the emerging armamentarium for the treatment of several retinal diseases.

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