

Clinical & Refractive Optometry is pleased to present this continuing education (CE) article by Dr. Joseph A. Halabis entitled **Management of Anterior Segment Pain and Inflammation**. In order to obtain a 1-hour Council of Optometric Practitioner Education (COPE) approved CE credit, please refer to page 69 for complete instructions.

Management of Anterior Segment Pain and Inflammation

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INTRODUCTION

Anterior segment disease due to infection, endogenous inflammatory conditions, and trauma is manifested by signs and symptoms of pain and inflammation. Even relatively minor eye conditions may be associated with significant patient discomfort which may be underestimated by the examining doctor.¹ It is important to know that pain and inflammation are not disease entities, but rather, signs and symptoms that accompany certain diseases. Treatments therefore, are nonspecific in nature. The medications available and their therapeutic indications in the treatment of anterior segment inflammation and pain are discussed here.

PAIN AND INFLAMMATION

The purpose of pain is to alert the individual to noxious stimuli and to create avoidance of those factors so that tissue repair can occur.² The blink reflex secondary to corneal trauma is initiated by pain and serves to protect the eye from further injury. The side effects of pain, however, can be debilitating and counter-productive to healing.

The sensory nerve supply to the globe and ocular adnexa is through the ophthalmic division (V_1) of the trigeminal nerve. The cornea has a uniquely dense nociceptive innervation. The non-ocular distribution of the ophthalmic division supplies various intracranial structures.³ This is of clinical importance because disease affecting these structures may cause "referred" pain to the eye and orbit. The maxillary division (V_2) supplies the lower lid through the infraorbital branch.

The inflammatory response is critical to the defense against invading micro-organisms and for healing. A discussion of inflammation would be incomplete without a brief review of the arachidonic acid pathway. Metabolites of the arachidonic acid pathway affect a variety of

biological processes, including inflammation. Mechanical, chemical, and physical stimuli cause cell membrane phospholipids to release arachidonic acid. Arachidonic acid is metabolized by phospholipase A_2 via the cyclooxygenase pathway and the lipoxygenase pathway.

Prostaglandins are the predominant product of the cyclooxygenase pathway and are mediators of the classic signs of inflammation, such as, erythema, increased vascular permeability, edema, and pain. Specifically, they are responsible for several pharmacological effects within the eye, including, miosis, the breakdown of the blood-aqueous-barrier and changes in intraocular pressure (IOP).⁴ The main product of the lipoxygenase pathway are leukotrienes. Leukotrienes are potent chemotactic agents and cause aggregation of neutrophils. Clinically, prostaglandins and leukotrienes are responsible for the symptoms of pain and itching and the signs of anterior chamber cell and flare and injection of the globe.

CYCLOPLEGICS

Ciliary spasm occurs as a result of inflammation in the ciliary body and from retrograde axonal reflex secondary to inflammation in the iris and cornea.⁵ Cycloplegic agents place the ciliary body and iris at rest alleviating pain and photophobia. They also stabilize the blood-aqueous-barrier reducing cell and flare. The primary utility of cycloplegic and mydriatic agents in uveitis therapy, however, is in preventing synechia formation and breaking recalcitrant synechia that have already formed. Mydriatic agents do not produce cycloplegia and possess no inherent anti-inflammatory activity but may be employed adjunctively to break formed synechia.

Table I lists the cycloplegic and mydriatic drugs that are commercially available. When choosing a cycloplegic for prophylaxis in the treatment of uveitis, it is important to remember that some iris movement is required to prevent synechia. A strong dilating agent like atropine, that produces a fixed and dilated pupil, may promote synechia formation in the dilated state. Not all cases of uveitis carry a risk of synechia. Those cases with a significant amount of fibrin should be managed more aggressively. Synechia formation during the course of uveitic therapy indicates inadequate treatment.

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Drug	Strength	Mydriasis		Cycloplegia	
		peak (min)	recovery (days)	peak (min)	recovery (days)
tropicamide	0.5,1	20-40	0.25	20-35	<0.25
cyclopentolate	0.5,1,2	30-60	1	25-75	0.25-1
homatropine	2,5	40-60	1-3	30-60	1-3
scopolamine	0.25	20-30	3-7	30-60	3-7
atropine	1	30-40	7-10	60-180	6-12
phenylephrine	2.5,10	40-60	0.25	n/a	n/a

Typically, scopolamine 0.25% or homatropine 5%, administered two to three times daily, is useful in moderate to severe forms of uveitis. Stronger agents should be prescribed if poor compliance is anticipated. The cycloplegic can be discontinued after the symptoms abate and the risk of synechia no longer exists.

CORTICOSTEROIDS

Prior to 1950, ocular inflammation was treated with atropine, heat, and salicylates. Then, Mann and Markson⁶ described the resolution of a case of uveitis and episcleritis with a tapering dose of pituitary adenocorticotrophic hormone (ACTH). Other reports followed.⁷ Topical corticosteroids became widely available in the 1960s for ophthalmic practice and are now the mainstay of treatment of ocular inflammation.

The anti-inflammatory effect produced by corticosteroids is in part due to inhibition of the phospholipase A₂ enzyme blocking the production of prostaglandins and leukotrienes. Corticosteroids also exert anti-inflammatory effects not directly involved in the arachidonic acid cascade. Specifically, corticosteroids potentiate epinephrine vasoconstriction, stabilize lysosomal membranes, exert effects on white blood cells, and decrease antibody production.⁸ Their ability to inhibit fibroblastic proliferation and vascularization and decrease scarring is especially important in ophthalmic applications where a clear cornea is essential. Corticosteroids are indicated for ocular inflammation and allergy, chemical and thermal trauma, and post-operative care.

Steroids and Intraocular Pressure

The clinical use of topical corticosteroids is not without risk of potentially serious side effects. The most commonly encountered of these is increased intraocular pressure in predisposed individuals, so-called “steroid responders.” Reports of steroid-induced glaucoma appeared soon after use of these agents became widespread.^{9,10} The same steroid-binding receptors that reside in the cornea, sclera, iris, and ciliary body also reside in the trabecular meshwork. While the exact mechanism is not known, it is thought that there is an increased resistance to aqueous humor outflow. It has long been

realized that agents with better ocular penetration have greater anti-inflammatory activity, but also greater potential to elevate IOP.¹¹ Prednisolone and dexamethasone, considered very effective medications, carry the greatest risk for pressure response.

“SOFT STEROIDS”

The risk of “steroid response” has prompted the development of new topical steroids that retain anti-inflammatory activity but have a low propensity to IOP.

Studies have shown that the acetate derivative of topical steroids is more effective in suppressing inflammation than the phosphate derivative or the alcohol base.¹² Flouromethalone, moderately effective in the alcohol base, is now available in the acetate derivative. It has been shown to be significantly more effective than flouromethalone alcohol and not significantly different than prednisolone acetate in therapeutic effect.¹³

Rimexolone has demonstrated a lower pressure elevating potential. When studied in known “steroid responders,” rimexolone demonstrated significantly less pressure elevation and a longer time for pressure response as compared to dexamethasone and prednisolone.¹⁴ Rimexolone is an ophthalmic suspension that resuspends with minimal shaking. It has demonstrated efficacy in the treatment of inflammation secondary to cataract surgery and is the first topical corticosteroid to be FDA approved for such use.¹⁵ In the treatment of uveitis, rimexolone was as effective in reducing cell and flare as prednisolone acetate.¹⁶

Loteprednol is from a new generation of “site active” topical corticosteroids. This drug has a high affinity for glucocorticoid receptors but is predictably converted to inactive metabolites. The trabecular meshwork is exposed to less active drug and therefore the potential to elevate pressure is less.

It is important to be aware of the potential for a pressure response when prescribing steroids, but this risk versus the benefit of the medication must be kept in perspective. The advent of the “soft steroid” does not mean that prednisolone and dexamethasone are obsolete. There are a number of ways to effectively address the issue of “steroid response.” The choice of steroid should be based on efficacy of the medication in view of the inflammation.

In those individuals that are susceptible to the pressure elevating effects of steroids, there is generally a latency of several weeks before this elevation in pressure occurs. In many conditions, short-term treatment is indicated and the treatment regimen may be completed before the pressure response is realized. If longer therapy is required, rimexolone, which has been shown to have a significantly longer IOP response time, can be prescribed. Finally, if an increase in pressure does occur, the drug can be tapered, glaucoma medications can be added, or the drug can be

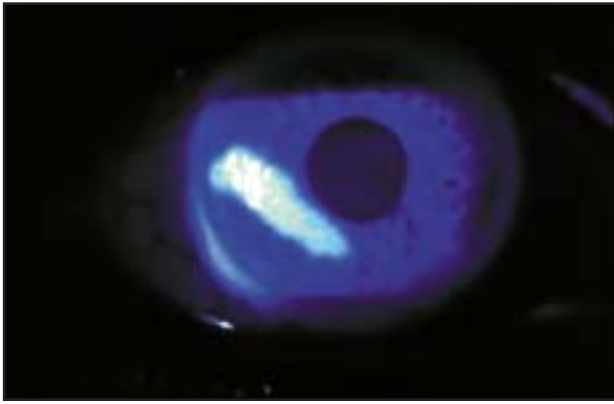


Fig. 1 Steroid-enhanced dendritic ulcer following 10-day use of steroid-antibiotic drops. Lesion had been treated in an emergency room as a suspected corneal abrasion.

substituted for one that has less pressure raising potential. It is imperative that pressure be measured prior to initiating therapy and monitored at each visit.

Other Side Effects

Topical corticosteroids have been associated with the formation of posterior subcapsular cataracts, retardation of epithelial wound healing, and a tendency to aggravate bacterial, fungal, and viral infections. The most serious of these is reactivation of herpes simplex keratitis (Fig. 1). Corticosteroids are contraindicated in the presence of herpes simplex epithelial disease because local tissue immunity is suppressed by these agents which can potentiate the infection.

Clinical Considerations

Prescribing corticosteroid medications for ocular disease constitutes palliative therapy. This mandates that an accurate diagnosis be made if these agents are to be used. Treating inflammatory signs and masking symptoms is valuable in preventing sequelae of inflammatory conditions and in making the patient comfortable. Corticosteroids have tremendous value in treating a variety of ocular inflammations, yet some clinicians are reluctant to use them because of the potential adverse effects. Because of this, some will use less effective measures, such as the nonsteroidal anti-inflammatory drugs (NSAIDs), to the detriment of the patient. New corticosteroids with fewer adverse effects coupled with a better understanding of the indications, risks, and benefits of corticosteroids will help clinicians incorporate these powerful anti-inflammatory medications into practice.

When initiating therapy it is important to treat aggressively and then slowly withdraw the medication

when the inflammation is brought under control. This is especially important when treating uveitis where inadequate treatment may result in a protracted course. A typical regimen for uveitis may be hourly drops while awake for the first few days to one week, tapered to every two hours for one week, every four hours for one week, four times daily for one week, three times daily for one week, twice daily for several days, once daily for several days, then discontinued. Less frequent dosing is suitable for mild inflammations and tapering is not required if used for a week or less.

Steroid-antibiotic combinations should be used when a corticosteroid is required and there is an infectious component or risk of infection. Corneal inflammation secondary to staphylococcal exotoxin is a prime example. These medications are commonly prescribed for post-operative prophylaxis and in cases of nonspecific conjunctivitis.

Anterior Uveitis

Anterior uveitis accounts for over 90% of the uveitis in primary care eye practice and can be associated with cataract, glaucoma, synechia, macular edema and neovascularization.¹⁷ The appropriate evaluation should begin with a complete ocular assessment including a dilated fundus examination. Systemic disease can be associated with uveitis and should be considered, however, an underlying etiology is often times never identified.

The mainstay of therapy in anterior uveitis remains topical corticosteroids. They effectively control the signs of cell and flare and the common rise in intraocular pressure secondary to trabeculitis. Topical nonsteroidal anti-inflammatory drugs are effective in treating post-operative inflammation, but their role in endogenous anterior uveitis remains unclear.

Steroids and Herpes Virus

Corticosteroids are contraindicated in the presence of herpes virus epithelial keratitis, but their use in the acute phase of stromal disease has been controversial. To resolve this issue, The Herpetic Eye Disease Study Group evaluated the use of prednisolone phosphate in a tapering dose with concomitant trifluridine over a ten week treatment period.¹⁸ This study showed that patients receiving corticosteroids improved more rapidly than those with placebo. This now provides a basis for the judicious use of corticosteroids with an antiviral umbrella in the treatment of acute stromal keratitis.

NONSTEROIDAL ANTI-INFLAMMATORY DRUGS

The most widely recognized pharmacologic action of the NSAIDs is cyclooxygenase inhibition in the arachidonic acid pathway which blocks the production of prostaglandins, which are mediators of inflammation and

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Table II Topical NSAIDs	
Topical NSAID	FDA-Approved Indication
flurbiprofen (<i>Ocufen</i>)	inhibition of intraoperative miosis
ketorolac (<i>Acular</i>)	seasonal allergic conjunctivitis, post-operative inflammation after cataract surgery
diclofenac (<i>Voltaren</i>)	post-operative inflammation after cataract surgery, photophobia after RK

pain. Now available in topical preparations, clinicians can prescribe these for ophthalmic indications without incurring the systemic side effects of oral routes. Indomethacin was the first commercially obtainable topical NSAID and is available in Europe and other parts of the world. There are three agents marketed in the United States: flurbiprofen (*Ocufen*), diclofenac (*Voltaren*), and ketorolac (*Acular*). Table II shows the FDA-approved indications of these medications. In addition, they have shown utility in the prevention and treatment of cystoid macular edema after cataract surgery.¹⁹ Because these agents have no effect on prostaglandins once formed, they are prescribed prior to the procedure and then continued postoperatively.

A major advantage over topical corticosteroids is the lack of the significant undesirable side effects. These include exacerbation of herpes simplex virus keratitis and other infections, posterior subcapsular cataract formation, and increased intraocular pressure. In addition, they do not inhibit corneal re-epithelialization.²⁰ These advantages have tempted clinicians to use these medications in place of corticosteroid drops. There is however, some concern that selective inhibition of the cyclooxygenase pathway may divert arachidonic acid to an increase in production of leukotrienes, which are chemotactic for white cells. This can result in the formation of corneal infiltrates following excimer PRK.²¹ For this reason, NSAIDs should not be used for extended periods without concomitant corticosteroids.

A major clinical utility of these medications is their ability to decrease pain. The analgesic property is due to a decrease in prostaglandins, an increase in beta-endorphin production, and depression of corneal nerve conduction. Efficacy of topical NSAIDs in the treatment of pain associated with refractive surgery has been well documented.²² These drugs may then be of benefit in treating the pain associated with other corneal conditions and anterior segment diseases.

A now defunct generic topical diclofenac product has been associated with indolent corneal ulceration and corneal melts.²³ This association has generated a renewed interest in the safety profile of all topical NSAIDs and a

review of clinical indications. Cases involving brand diclofenac and ketorolac were more likely to have received high doses or to have been associated with ocular comorbidity. The use of these agents should be avoided in the presence of pre-existing corneal inflammation.²⁴

“Off-Label” Uses

The list of FDA-approved indications of the topical NSAIDs is rather limited, but their utility in so-called “off-label” clinical applications is expanding. The full scope of such applications is yet to be realized. In the United States the FDA administers the Federal Food, Drug, and Cosmetic Act (FDCA) of 1938. The FDCA mandates that new drugs demonstrate safety and efficacy before being approved. The FDA regulates the pharmaceutical industry but not the practice of medicine. Therefore, once approved, clinicians, as part of the practice of medicine, are free to prescribe an approved drug for any purpose that they deem appropriate, as long as the use is not contraindicated.²⁵ However, pharmaceutical manufacturers may not market, promote, or advertise the use of approved medications for anything other than the approved indications.

It becomes impractical to require approved drugs to undergo separate randomized clinical trials and be approved for every new use. This is especially true if the drug has already demonstrated safety and efficacy for such use.²⁶ To substantiate the appropriate use of a medication in an “off-label” use, the clinician must extrapolate information from the package insert, consult with colleagues, and review the literature from refereed professional journals.²⁷ It is within the clinician’s ethical prerogative to utilize a medication for the treatment of a patient, as long as the clinician is convinced that the benefit outweighs the possible risk, and the use is not in the context of research.

Traumatic Corneal Abrasions

Traumatic corneal abrasion is a common clinical entity encountered in optometric practice where “off-label” use of NSAIDs may be useful. Patients experience significant ocular pain, photophobia, lacrimation, and decreased visual acuity until the epithelial defect heals. The corneal epithelium possesses a remarkable capability of regeneration by cell migration and proliferation. Abrasions usually heal within 24 to 48 hours.²⁸ Treatment is aimed at eliminating the patient’s discomfort while promoting resolution of the epithelial defect.

The treatment of traumatic corneal abrasions has traditionally involved topical antibiotic drops or ointment, cycloplegia, and a pressure patch. The use of pressure patching has fallen into disfavor. Blinking, which is eliminated by patching, was originally thought to retard

healing by hindering epithelial attachment to the underlying basement membrane. This does not appear to be a significant factor in healing.²⁹

Pressure patching holds several distinct disadvantages. With the patch in place, the patient is rendered monocular, delaying a return to normal daily activities. In addition, a pressure patch limits tear exchange and creates a warm moist environment that decreases corneal oxygen, which may slow epithelial healing and predispose to secondary infection.³⁰ *Pseudomonas* corneal ulcers have been reported following patching of corneal abrasions associated with contact lens wear.³¹ Patching is specifically contraindicated in abrasions associated with contact lens wear. Kaiser,³² in a large, randomized, prospective trial to evaluate the effectiveness of pressure patching in the treatment of traumatic abrasions found that patients healed significantly faster and experienced less pain and fewer subjective complaints when they did not receive a pressure patch.

Topical NSAIDs and soft contact lenses have been shown to reduce the pain secondary to the corneal abrasions following laser photorefractive keratectomy.^{33,34} This experience has stimulated an interest in applying these modalities to the treatment of traumatic corneal abrasions. Donnenfeld et al,³⁵ in a randomized, prospective clinical trial compared the efficacy of pressure patching, a bandage contact lens, and a bandage contact lens with a topical NSAID (0.5% ketorolac tromethamine) in the treatment of traumatic abrasions. The group that received both the contact lens and the topical NSAID showed a significant decrease in pain. Both groups receiving the contact lens were able to return to normal activities in a shorter period of time. There was no significant difference in the healing time of the abrasion of the three groups.

The use of a bandage contact lens in the treatment of traumatic abrasion is not without potential complications, the most devastating of which is bacterial keratitis. In an effort to eliminate the risks associated with a bandage contact lens, some authors advocate the use of a topical NSAID, without a contact lens, as adjunctive therapy in the treatment of traumatic corneal abrasions.^{36,37} Finally, the use of bandage contact lenses and topical NSAIDs incurs greater cost. These factors must be weighed against the patients short-term visual needs in determining a treatment plan.

CONCLUSION

Pain and inflammation are common features of anterior segment conditions. Ocular pain is often accompanied by patient anxiety and offers a unique clinical challenge in optometric practice. The topical medications now available provide the armaments required to effectively manage these conditions. □

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