

Topical Corticosteroid and NSAID Therapies for Ocular Inflammation

A concise overview for clinical practice.

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When beginning to prescribe anti-inflammatory medications, it is common to be confused with respect to the various preparations that are commercially available. What is the difference in potency between prednisolone, loteprednol, and difluprednate? How do I choose which nonsteroidal drop to use for my patient? In this second installment from Dr. Garrick Chak and colleagues, they review the basics and intricacies of ophthalmic steroidal and nonsteroidal formulations. Knowledge of the specifics detailed here will allow you to better tailor your medical management of patients. As always, if you have any recommendation for "Residents and Fellows," please let me know.

—Sumit "Sam" Garg, MD, section editor

Topical corticosteroids and nonsteroidal anti-inflammatory drugs (NSAIDs) are often used to treat ocular inflammation. An appreciation of the subtle differences may help physicians determine which medication to prescribe as they strive to offer patient-centered care.

PEARLS FOR TOPICAL CORTICOSTEROIDS

Topical ophthalmic corticosteroid agents can be classified as ketone steroids (prednisolone, difluprednate, dexamethasone, fluorometholone, and rimexolone) or ester steroid (loteprednol) based on pharmacologic design. Loteprednol is formulated with an ester instead of a ketone group at the C-20 position.¹ Thought to be cataractogenic, the C-20 ketone group forms a covalent bond with lens proteins that are found only in steroid-induced cataracts.¹ Although this is a widely accepted hypothesis for steroid-induced cataracts, other mechanisms may exist.

In clinical practice, corticosteroids are often grouped broadly by anti-inflammatory potency, defined as the binding affinity of the drug to the glucocorticoid receptor. As a brief review, the corticosteroid binds to a glucocorticoid receptor that is located in the cytosol. Once bound, the glucocorticoid receptor is activated and migrates into the nucleus, where it modulates signaling pathways and protein expression (more than 5,000 genes are targeted

via corticosteroids).² Corticosteroid therapies disrupt the inflammatory cascade by inhibiting the release of arachidonic acid from cell membrane phospholipids, thus preventing the formation of prostaglandins (cyclooxygenase [COX] pathway) as well as leukotrienes and other inflammatory mediators (lipoxygenase pathways).

EFFICACY VERSUS POTENCY

The anti-inflammatory potency of a drug is a pharmacologically relative term—in some instances relative to hydrocortisone³ and in other instances relative to dexamethasone⁴—and is not necessarily tantamount to its clinical efficacy topically. For instance, topical dexamethasone alcohol 0.1% is known to have a sixfold higher potency and double the half-life of topical prednisolone acetate 1% (Table 1). Even so, the latter attained a peak aqueous concentration that was more than 21 to 36 times higher than the former and also persisted with a detectable drug aqueous concentration after 24 hours (whereas the former was undetectable) because of superior penetration of the drug.⁵ Thus, when selecting the appropriate corticosteroid for the patient, the eye care provider should note that the efficacy of a topical corticosteroid comprises a combination of variables such as potency, vehicle, drug concentration, duration of action, and ocular penetration.

TABLE 1. TOPICAL CORTICOSTEROIDS IN THE UNITED STATES

| Topical Potency (Clinical Efficacy) | Name | Anti-inflammatory Potency (Relative to Hydrocortisone) | Average IOP Rise, mm Hg | Half-life of Drug, hrs |
|-------------------------------------|-------------------------|--|---|-----------------------------|
| Highest | Difluprednate | 60 | 17.8 | 2x as long as betamethasone |
| Highest | Prednisolone acetate | 4 | 10.0 + 1.7 | 18-36 |
| Higher | Dexamethasone acetate | 25 | 22.0 + 2.9 | 36-54 |
| Higher | Prednisolone phosphate | 4 | | 18-36 |
| High | Loteprednol etabonate | 25 | 1.7% with spike > 10 mm Hg (901 patients) | |
| Moderate | Rimexolone | 25 | 2% with spike > 10 mm Hg (98 patients) | |
| Moderate | Dexamethasone phosphate | 25 | | 36-54 |
| Moderate | Fluorometholone acetate | 40-50 | 6.1 + 1.4 | |
| Mild | Medrysone | | 1.0 + 1.3 | |
| Mild | Fluorometholone alcohol | 40-50 | | |
| Low | Hydrocortisone | 1 | 3.2 + 1.4 | 8-12 |
| Low | Cortisone | 0.8 | | 8-12 |

SOLUBILITY, PENETRATION, AND CONVENIENCE

Within a class of corticosteroids, the acetate, the phosphate, or the alcohol form—somewhere in between acetate and phosphate in the solubility spectrum—gives physicians an idea of the drug's propensity for corneal penetration and may change the relative anti-inflammatory efficacy of the drug. Aqueous humor samples have shown that prednisolone acetate achieves higher drug concentrations than prednisolone sodium phosphate in the presence of an intact corneal epithelium.⁶ The acetate form is more lipophilic and available as a suspension, which leads to longer contact time and better penetration. The phosphate form is more hydrophilic, however, and is available as a solution. Topical prednisolone sodium phosphate 1% is less effective than topical prednisolone acetate 1% due to bioavailability and penetration (lower ability to achieve high aqueous humor concentration of the drug through an intact corneal epithelium).⁷

Generally, a suspension (for instance, prednisolone acetate) must be shaken vigorously for the medication to be homogenous upon application,⁸ whereas a solution (eg, prednisolone sodium phosphate), an emulsion

(eg, difluprednate), or a gel (eg, loteprednol etabonate) removes this responsibility from those who find shaking agitating. Even among prednisolone acetate suspensions, a generic version has been shown to have poorer dose uniformity and may require more shaking in order to achieve the same dose uniformity as a brand-name version.⁹ Besides the convenience of not requiring shaking, difluprednate 0.05% does not contain benzalkonium chloride (BAK); instead, it uses sorbic acid as a preservative. Alternative topical corticosteroids without BAK include preservative-free dexamethasone 0.1%, preservative-free loteprednol 0.5%, and compounded preservative-free methylprednisolone 1%. Table 1 provides a quick reference list of topical corticosteroids that are frequently prescribed in the United States.¹⁰⁻¹⁴

RISK AND REWARDS, IOP ELEVATION

With corticosteroid therapy, higher anti-inflammatory rewards do not come without the potential for higher risk, such as IOP elevation, cataractogenesis, epithelial breakdown into a geographic ulcer if administered in the presence of a herpetic dendritic ulcer, and fungal infection with long-term corticosteroid use. Generally, the risk

TABLE 2. NSAIDs IN THE UNITED STATES

| Drug | Brand Name | Manufacturer | Dosing | COX-2 IC50, μm | Preservative |
|--------------|-------------------------|---|--------|---------------------------|------------------------------------|
| Bromfenac | Xibrom 0.09% | Formerly Ista Pharmaceuticals; now generic | b.i.d. | 0.023 | Benzalkonium chloride (BAK) 0.005% |
| | Bromday 0.09% | Bausch + Lomb | Daily | | BAK 0.005% |
| | Prolensa 0.07% | Bausch + Lomb | Daily | | BAK 0.005% |
| Diclofenac | Voltaren 0.1% Ophtha CD | Alcon | q.i.d. | 0.085 | BAK 0.005% |
| | Voltaren 0.1% Ophtha | Alcon | q.i.d. | | Thimerosal 0.004% |
| | Dicloftil 0.1% | Farmigee (not available in the United States) | q.i.d. | | Preservative free |
| Flurbiprofen | Ocufen 0.03% | Allergan | q.i.d. | 0.102 | Thimerosal 0.005% |
| Ketorolac | Acular 0.5% | Allergan | q.i.d. | 0.12 | BAK 0.01% |
| | Acular LS 0.4% | Allergan | q.i.d. | | BAK 0.006% |
| | Acuvail 0.45% | Allergan | b.i.d. | | Preservative free |
| Nepafenac | Nevanac | Alcon | t.i.d. | 0.15 | BAK 0.005% |
| | Ilevro | Alcon | Daily | | BAK 0.005% |

for a steroid-related IOP spike is correlated to the potency of the topical steroid; other influencing factors include the duration and frequency of the drug's administration as well as the susceptibility of the individual.

About one-third of the general population are potential moderate steroid responders (IOP increase of 6-15 mm Hg). About 5% to 6% of the general population, in addition to the 33% mentioned previously, are severe responders (IOP increase > 15 mm Hg with many having a marked IOP increase of > 31 mm Hg after 4-6 weeks of topical steroid use).^{15,16} Despite proper tapering of topical corticosteroid therapy, IOP may not necessarily decrease in steroid-responsive patients who are at increased risk of developing open-angle glaucoma. Also, topical corticosteroids may yield a crossover effect with IOP elevation in the fellow eye from systemic absorption.¹⁷ The provider should be aware that corticosteroid use may lead to a dose-dependent IOP spike that occurs more frequently, more severely, and more rapidly in children than in adults.¹⁸

Due to the potential IOP elevation with the stronger corticosteroids, "softer" corticosteroids have been strategically designed to reduce the risk of IOP elevation. Loteprednol and rimexolone are rapidly hydrolyzed into their respective inactive metabolite, and fluorometholone—despite a surprisingly high pharmacologic potency—is considered a soft steroid because of its limited corneal penetration.⁵ Placebo-controlled trials have been

conducted, but there has not been a randomized head-to-head comparison of the softer steroids.

By knowing the profile of each corticosteroid, an ophthalmic provider can select the most appropriate anti-inflammatory medication for the patient.

NSAID PEARLS

NSAIDs produce a variety of ocular effects. The growing body of scientific evidence suggests they may be beneficial in diabetic retinopathy, diabetic macular edema, age-related macular degeneration, and even ocular tumors. The longest-standing and most widespread uses of NSAIDs, however, are for reducing postoperative inflammation and preventing and treating cystoid macular edema (CME) associated with intraocular surgery. This article focuses on those applications.

NSAIDs reduce inflammation by inhibiting COX enzymes (COX-1 and COX-2), thereby limiting the production of prostaglandins via the arachidonic acid cascade. Prostaglandins mediate multiple inflammatory changes, increasing vasodilation and vascular permeability.^{19,20} In the eye, the drugs also disrupt the blood-aqueous barrier, leading not only to iritis but also increasing the risk of CME as inflammatory mediators leak into the eye. Topical NSAIDs have been shown to be more effective than corticosteroids in re-establishing the blood-aqueous barrier and can thus play a critical role in the management of postoperative

and other ophthalmic inflammation.²¹ When choosing an NSAID, several factors are worth considering.

EFFICACY

As a rule, the inhibition of COX-2—inducible in inflammatory conditions—determines the clinical efficacy of an ophthalmic NSAID (Table 2).^{22,23} Interestingly, however, evidence does not support a direct correlation between in vitro potency, measured by the IC₅₀ (the concentration required to reduce enzyme activity to half), and either bioavailability or medication effectiveness.²⁴ Flach et al compared the anti-inflammatory effects of diclofenac (IC₅₀ = 0.085 μm) and ketorolac (IC₅₀ = 0.12 μm) in a double-masked study of 120 postoperative patients using both a laser cell and flare meter and clinical observation. The investigators found the two treatments to be equivalent.²⁵ Bromfenac has the lowest IC₅₀ of the group (0.023 μm), indicating greatest potency. A 2007 study, however, compared the in vivo concentration and in vitro PGE₂ inhibition of amfenac, its prodrug nepafenac (nepafenac is converted to bioactive amfenac primarily by ocular tissue hydrolases²⁶), ketorolac, and bromfenac. Nepafenac proved to be most bioavailable with the shortest time to peak concentration and the highest peak aqueous humor concentration. Amfenac was more potent at COX-2 inhibition than either bromfenac or ketorolac (the most potent COX-1 inhibitor).²⁷

On the other hand, another study conducted that same year suggested ketorolac was as effective as nepafenac clinically (assessed using BCVA, anterior chamber inflammation on examination, and pain control) and perhaps better tolerated, with greater reported satisfaction and compliance among patients.^{28,29}

Although flurbiprofen reduces intraoperative miosis and inflammation after cataract surgery, the weight of the scientific evidence suggests it is less effective than other available NSAIDs.³⁰

DOSING SCHEDULE

While maximizing drug effect may be necessary in some patients (eg, those with persistent macular edema), in many routine cases, it is just as important that ease of drop use facilitates patients' adherence to therapy. Several studies have examined reduced dosing schedules for bromfenac, ketorolac, and nepafenac. Among dosing schedules for nepafenac, dosing three times a day resulted in better pain control on day 1 after cataract surgery. By postoperative day 3, patients using nepafenac only once daily were equally comfortable, however, and by day 14, there was no measureable difference in inflammation.²⁸ A more recent small study suggested that bromfenac administered just once daily was equivalent to nepafenac

dosed three times daily after cataract surgery, based on measures of anterior chamber inflammation, BCVA, macular volume/retinal thickness, and IOP.³¹ Twice-daily dosing of ketorolac has been evaluated versus placebo but not head-to-head with other agents.

SIDE EFFECTS

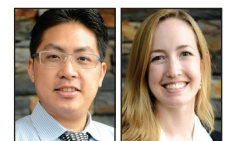
In the 1990s, reports of corneal melting associated with topical NSAID use caused significant concern in the ophthalmology community. Most cases were associated with a now-discontinued diclofenac product (DSOS) and felt to be related to the vitamin E-based solubilizer tocopherol it contained.^{32,33} However, a few cases of corneal melt have since been associated with other formulations of ophthalmic diclofenac. One proposed mechanism is depletion of the neuropeptide substance P within the corneal epithelium, which is associated with delayed wound healing and a risk of neurotrophic keratopathy.³⁴ It is also speculated that diclofenac increases the production of lipoxigenase-derived LTB₄, a polymorphonuclear chemotactic, leading to corneal inflammation and melting.³³

CONCLUSION

In general, the ophthalmic practitioner should consider the patient's profile when prescribing topical corticosteroids or NSAIDs. With corticosteroids, matching the penetration and potency of the drug with consideration of clinical context, contraindications, monitoring of the potential development of open-angle glaucoma, and the patient's physical limitations guides selection of the topical corticosteroid that is most appropriate for the patient. Before prescribing an NSAID, it behooves practitioners to determine whether a patient is predisposed to delayed wound healing (as in diabetes, rheumatoid arthritis, or other autoimmune inflammatory conditions) or has likely corneal denervation (as in severe ocular surface disease, a history of herpetic keratitis, or after multiple complex ocular surgeries). Certainly, as with topical steroids, patients should not follow a prolonged, unsupervised course of topical NSAIDs. ■

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