Supplement to

RETINA TODAY

March/April 2008

Clinical Cases: NSAIDs for CME

Treatment decisions are discussed.

By Michael D. Ober, MD

INTRODUCTION

Cystoid macular edema (CME) is a serious complication of intraocular surgery, which results in transient or even permanent vision loss. The incidence of acute, visually significant CME has been reported from 1% to 2% of patients following uncomplicated phacoemulsification.[1,2] A much greater proportion of patients (20%–30%) have been reported to have angiographic edema or edema based upon optical coherence tomography (OCT).[3-5]

Because it is believed to be secondary to inflammation, CME is treated with antiinflammatory agents. Corticosteroids are effective against macular edema due to a variety of mechanisms including the reduction of inflammatory mediators such as interleukin-5, interleukin-6, and interleukin-8; prostaglandins; interferon gamma; vascular endothelial growth factor and tumor necrosis factor alpha.[6-9] The antiinflammatory potency of corticosteroids is well appreciated, but their mechanism of action is still not fully understood. It has been shown that topical, subtenons, and intravitreal corticosteroids can effectively prevent and treat CME,[10-13] but are associated with serious ocular side effects especially cataracts, glaucoma, and infection.[14-19] For these reasons, less toxic alternative treatments are desirable.

The following case studies demonstrate how the use of alternative treatment with topical nonsteroidal antiinflammatory drugs (NSAIDs) can be an effective therapy for treating CME in two very different situations.

CASE #1: CME POSTVITRECTOMY

In April 2006 a 60-year-old woman presented to my office with a macular hole in her right eye (Figure 1). Visual acuity at presentation was 20/250. In early May, the patient underwent vitrectomy with membrane peel and gas injection for macular hole repair. A routine postoperative course of topical antibiotics (moxifloxacin; Vigamox, Alcon) and steroids (prednisolone acetate; Econopred Plus, Alcon) were prescribed.

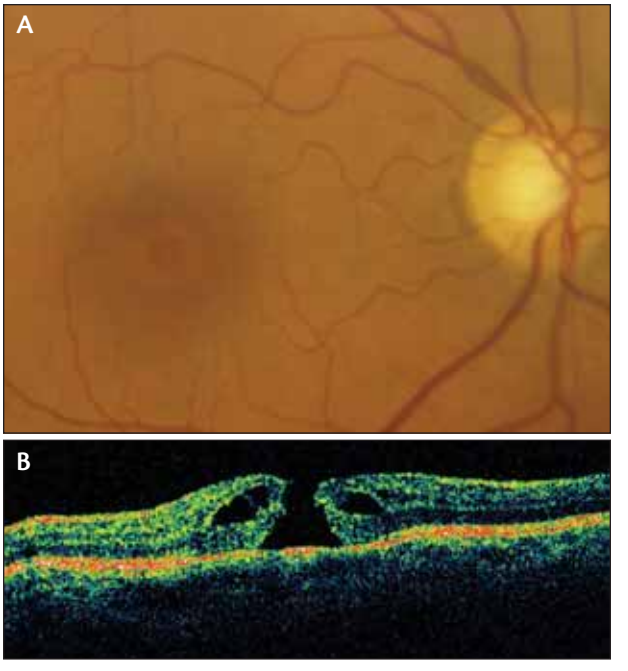

Figure 1. Case #1: Fundus photography (A) and OCT (B) of preoperative macular hole.

STEROID-INDUCED GLAUCOMA

On follow-up 10 days later, her intraocular pressure (IOP) was 42 mm Hg. She was immediately treated with dorzolamide hydrochloride-timolol maleate (Cosopt, Merck), brimonidine 0.15% (Alphagan P, Allergan), and travoprost (Travatan, Alcon). Despite treatment, the patient's IOP reduced only to 39 mm Hg, therefore oral acetazolemide was started

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STATEMENT OF NEED

Cystoid macular edema (CME) is a condition characterized by swelling of the retina due to leakage from the small blood vessels within the fovea, the central part of the retina responsible for your detailed vision. It is a general condition caused by a very wide range of retinal diseases which may include:

- diabetic retinopathy
- wet age-related macular degeneration or other causes of bleeding under the retina
- retinal vein occlusions
- epiretinal membranes (or macular pucker)
- uveitis other causes of inflammation within the eye such as recent eye surgery (such as cataract surgery)

Because many factors can lead to CME, effective treatment will vary. Retinal inflammation is usually treated with antiinflammatory medications. These are usually given as eye drops, though occasionally they must be administered as an injection or by mouth.

Topical NSAIDs have been shown to be effective in reducing postoperative cells and flares in many cataract patients. A small but significant portion of patients, however, will not have complete control of postoperative inflammation with a topical nonsteroidal alone. Therefore, using a combination of topical corticosteroids and topical NSAIDs is often most effective in enduring excellent control of inflammatory responses.

Many studies have suggested that topical NSAIDs are effective at preventing CME. In some studies, topical NSAIDs appear to be more efficacious than corticosteroids at preventing macular edema.

In light of increasing evidence for adequate, and sometimes improved, efficacy of NSAID monotherapy compared with corticosteroids, a postoperative regimen consisting solely of an NSAID may replace combination therapy as the primary regimen for CME prophylaxis.

TARGET AUDIENCE

This activity is designed for ophthalmologists who treat CME.

LEARNING OBJECTIVES

Upon successfully completing this learning program, participants should be able to:

- identify the currently available pharmaceutical agents used to treat CME
- discuss the mechanism of action of NSAIDs
- discuss the tolerability of steroids and NSAIDs
- discuss the data that support the treatment described in the cases presented.

METHOD OF INSTRUCTION

Participants should read the learning objectives and continuing medical education (CME) activity in its entirety. After reviewing the material, they must complete the self-assessment test, which consists of a series of multiple-choice questions. To answer these questions online and receive real-time results, please visit www.dulaneyfoundation.org and click "Online Courses." If you are experiencing problems with the online test, please e-mail us at support@dulaneyfoundation.org and explain the details of any problems you encounter with the Web site. Alternatively, you can fax your exam to us at +1 610 771 4443. Please note, in order to receive your certificate and credit when faxing your test you must include your full name as well as an e-mail address, as certificates will be issued electronically. Upon completing the activity and achieving a passing score of over 70% on the self-assessment test, you may print out a CME credit letter awarding 1 *AMA PRA Category 1 Credit.™*

The estimated time to complete this activity is 1 hour.

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CONTENT VALIDATION

In compliance with ACCME standards for commercial support and The Dulaney Foundation's policy and procedure for resolving conflicts of interest, this CME activity was peer reviewed for clinical content validity to ensure the activity's materials are fair, balanced and free of bias; the activity materials represent a standard of practice within the medical profession; and any studies cited in the materials upon which recommendations are based are scientifically objective and conform to research principles generally accepted by the scientific community.

FACULTY CREDENTIALS

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FACULTY DISCLOSURE DECLARATIONS

Dr. Ober states that he is a paid consultant for Alcon Laboratories, Genentech, OSI/Eyetech/Pfizer, and SensoMotoric Instruments.

Reviewer William Trattler, MD, states that he has received grant/research support from Lenstec, Glaukos, Ista, Allergan, AMO and Rapid Pathogen Screenings. He is a consultant for Allergan and on the speakers bureau for Ista, Allergan, and AMO.

Alan Guralnick and Rachel Renshaw state that they have no financial relationships to disclose.

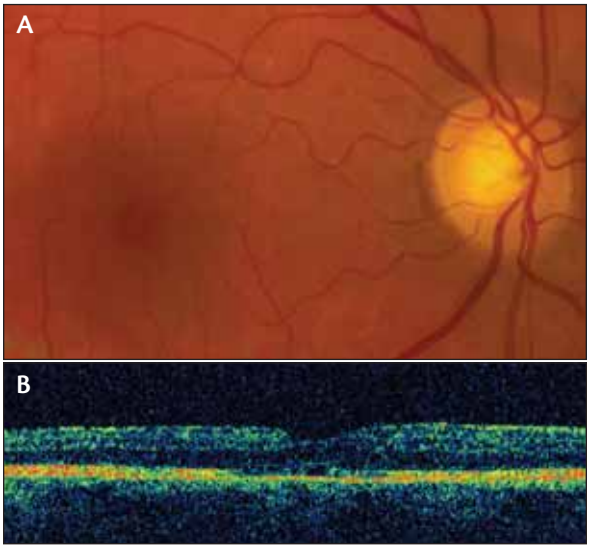

Figure 2. Case #1: Fundus photo (A) and OCT (B) postvitrectomy shows closed macular hole and no signs of CME.

and the topical prednisolone was discontinued. Two days later, the IOP measured 14 mm Hg and the pressure-lowering medications were reduced to timolol 0.5% and brimonidine.

In January 2007, the patient's vision measured 20/40. The IOP measured 14 mm Hg while continuing timolol 0.5% and brimonidine. OCT showed that the macular hole was closed and there were no signs of CME (Figure 2). The patient was instructed to continue dosing with timolol and brimonidine and return to her referring physician.

CME AND REDUCED VISION

In October 2007 I was contacted by the patient's referring physician. She had undergone cataract surgery on June 27 with improvement in vision, but noticed a recent decline. Visual acuity had decreased to 20/80 and CME was detected on exam. OCT confirmed the CME with central retinal thickness measurement of 674 µm. Given her history of steroid response, I felt strongly that we try an alternative to a corticosteroid. Nepafenac (Nevanac, Alcon) was prescribed three times daily. When she returned to my office 6 weeks later, vision was 20/70 and notably improved per the patient. IOP was 16 mm Hg and OCT examination showed improvement in central retinal thickness measurement to 489 µm (Figure 3). Given these results, we continued nepafenac drops 3 times daily.

On December 28, her vision had improved to 20/50+ and IOP remained at 16 mm Hg on timolol and brimonidine. The CME had improved further on

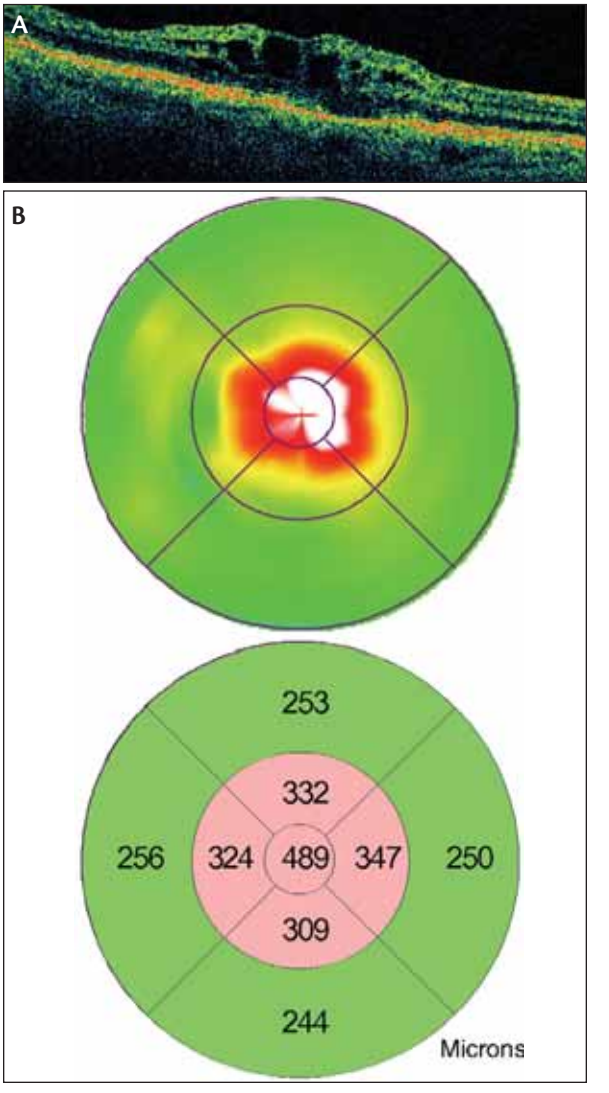

Figure 3. Case #1: After 6 weeks with nepafenac therapy OCT (A) examination showed improvement in central retinal thickness measurement to 489 µm (B).

OCT with a central thickness of 387 µm. Cystic changes were seen in the perifoveal retina, so nepafenac was continued. In February 2008, the patient's visual acuity has improved further to 20/40+ and IOP measured 19 mm Hg. Retinal thickness decreased an additional 69 µm to 318 µm (Figure 4). Nepafenac has been continued, as the CME has improved, but has not completely resolved.

CASE #2: CME POSTCATARACT SURGERY

A 79-year-old woman underwent complicated cataract surgery in the left eye with placement of an

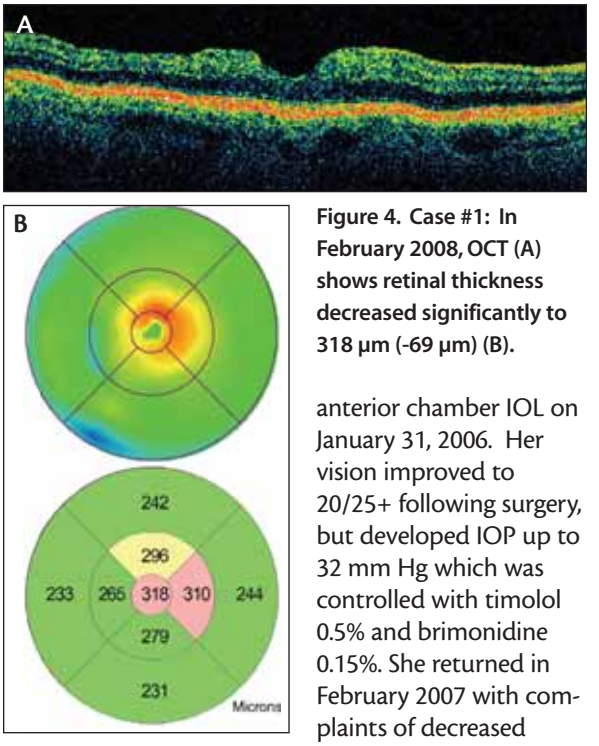

Figure 4. Case #1: In February 2008, OCT (A) shows retinal thickness decreased significantly to 318 µm (-69 µm) (B).

anterior chamber IOL on January 31, 2006. Her vision improved to 20/25+ following surgery, but developed IOP up to 32 mm Hg which was controlled with timolol 0.5% and brimonidine 0.15%. She returned in February 2007 with complaints of decreased vision, which measured 20/60 in the left eye (Figure 5). The patient was placed on flurbiprofen (Ocufen, Allergan) and prednisolone (Predforte, Allergan) in addition to her timolol and brimonidine which led to increased IOP. In response, prednisolone was changed to loteprednol etabonate (Lotemax, Bausch & Lomb) and timolol was exchanged for dorzolamide hydrochloride-timolol (Figure 6).

She remained on this treatment for several months during which the IOP remained elevated and vision improved, but was fluctuating, according to the patient. In August of 2007, the patient presented to my office. Her vision measured 20/30 with an IOP of 26 mm Hg and CME evident on examination. OCT confirmed intraretinal cystic changes and subfoveal fluid with a central retinal thickness of 367 µm (Figure 7). Loteprednol etabonate and flurbiprofen were discontinued and she was started on nepafenac three times per day. Six weeks later, vision improved to 20/25+, IOP reduced to 18 mm Hg, and OCT showed resolution of edema and fluid with a central retinal thickness measuring 232 µm (Figure 8). Nevanac was discontinued in November 2007 at which time vision measured 20/25+, IOP was 16 mm Hg, and OCT showed no retinal edema.

OUTCOMES

The above cases demonstrate that nepafenac can be efficacious treatment for CME in patients status

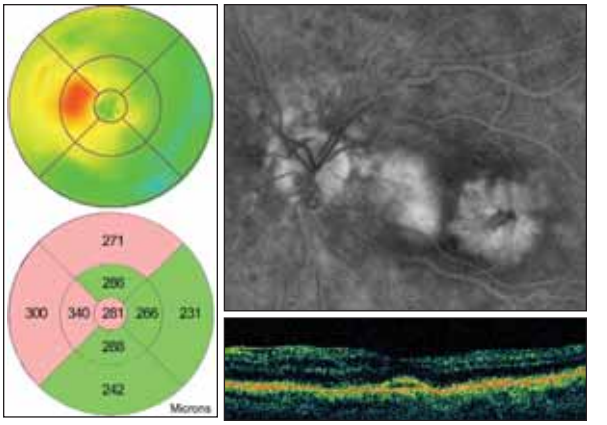

Figure 5. Case #2: Increased retinal thickness corresponds with decrease in visual acuity.

post-vitrectomy and/or those who have partially responded to other NSAIDs. These complicated cases are frequently difficult to treat, often requiring peri- or intraocular steroids and leading to elevated IOP, especially in patients such as above with a known history of steroid-induced glaucoma. I believe it is important to use topical NSAIDs for the treatment of CME prior to considering steroid injections, given their relative side-effect profiles.

DISCUSSION

Nonsteroidal antiinflammatory drugs prevent prostaglandin synthesis from arachidonic acid through the inhibition of cyclooxygenase. Diclofenac 0.1% (Voltaren, Merck),[20,21] ketorolac 0.5% (Acular, Allergan),[22-24] flurbiprofen,[3,25] and indomethacin[3,25,26] have all demonstrated prophylactic activity against CME in randomized, placebo-controlled trials. In addition to CME prevention, NSAIDs have been shown to effectively treat both acute and chronic CME.[27-30] Corticosteroids inhibit prostaglandin synthesis by a different mechanism than do NSAIDs and therapy combining the two has been shown to be more efficacious than monotherapy.[31] It is now fairly standard practice to initiate a combination of NSAID and steroid upon documentation of clinical pseudophakic CME.[32]

PENETRATION OF NSAIDS

All topical NSAIDs penetrate the cornea to exert their biologic activity against CME. Nepafenac is unique in that it is a prodrug which is converted to its active form, amfenac, by enzymatic hydrolases. The prodrug form is neutral (noncharged) which is believed to result in greater corneal permeability than the acidic structures in conventional NSAIDs. Indeed, one in vivo phar-

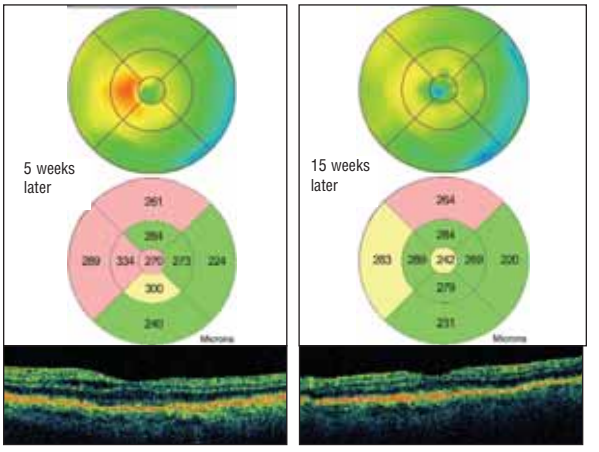

Figure 6. Case #2: Retinal thickness improves over 15 weeks with flurbiprofen corresponding increase in visual acuity.

macodynamic studies comparing nepafenac, ketorolac, and bromfenac have shown that nepafenac 0.1% reached anterior chamber aqueous concentrations 3.6 times higher than ketorolac 0.4% and eight times higher than bromfenac.[33] The time to greatest concentration was also shortest for nepafenac signifying faster penetration. One animal study found a sixfold greater corneal penetration and for nepafenac vs diclofenac as well as more rapid penetration.[34] There is very little conversion of nepafenac to amfenac within the cornea allowing full, rapid penetration into the eye of the prodrug. The majority of conversion occurs in the iris/ciliary body and retina/choroid.[34] The high intraocular concentration of nepafenac may act as a reservoir for continued production of amfenac. Intraocular levels of amfenac were found to lag behind nepafenac[33] and likely remain for a greater period of time. A rabbit model showed that a single application of nepafenac resulted in significant bioactivity 8 hours later.[35]

EFFICACY OF NSAIDS

The efficacy of NSAIDs is correlated with their ability to reduce the production of prostaglandins by inhibiting cyclooxygenase (COX). Cyclooxygenase comes in two major forms, COX 1 is present within normal tissues and associated with normal functions while COX 2 is an induced enzyme which is responsible for prostaglandin production during injury and/or inflammation.[36] In vivo studies have shown that amfenac has more potent COX-2 inhibition than bromfenac, and ketorolac, while ketorolac has the most potent COX-1 inhibition.[33] Amfenac also has the greatest COX-2/COX-1 inhibitory ratio.[33] Another study showed that amfenac had significant activity against both COX-1

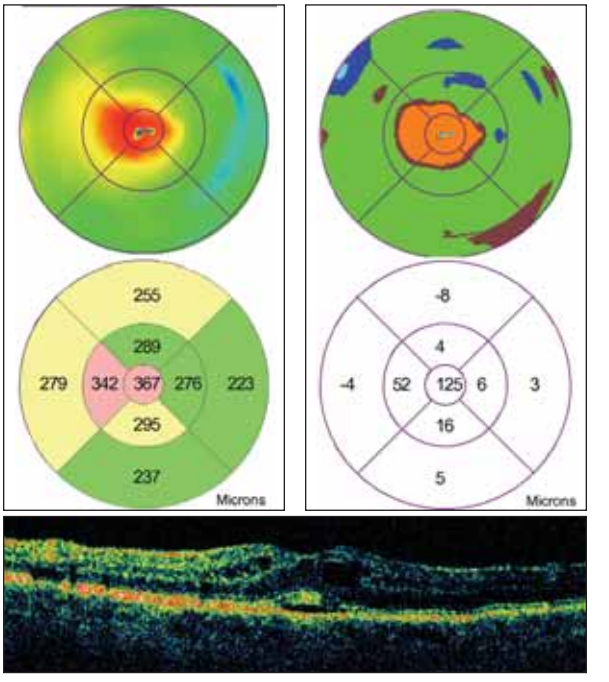

Figure 7. Case #2: Symptomatic decrease is seen on OCT. Nepafenac three times daily was initiated.

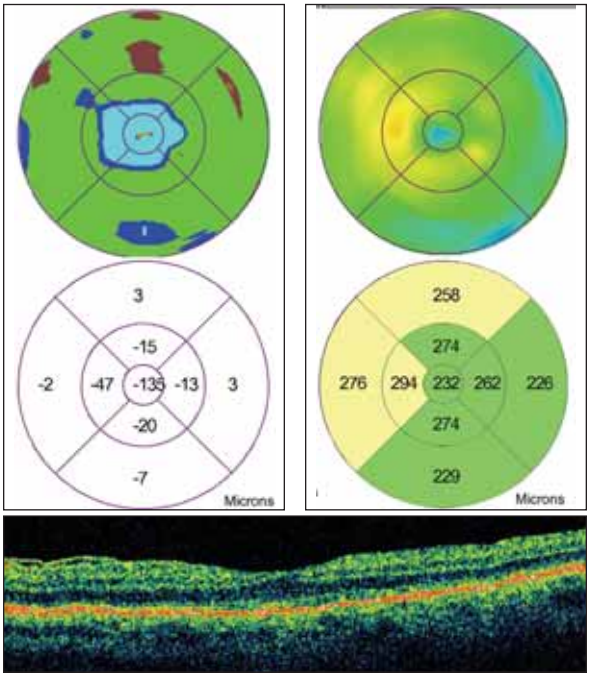

Figure 8. Case #2: OCT (bottom) shows the resolution of CME with improved retinal thickness measurements.

and COX-2.[35] Bucci et al analyzed samples of prostaglandin E2 (PGE2) at the time of cataract surgery for patients treated with ketorolac or nepafenac 2 days

prior. They concluded that ketorolac inhibited PGE2 significantly greater than nepafenac.[37] A separate study comparing PGE2 levels at the time of cataract surgery receiving preoperative NSAID drops showed highly variable results with no interpretable data and concluded that PGE2 takes 1 to 2 hours to be produced, which implies that values collected at the time of cataract surgery in this particular study represent baseline and thus are of little relevance.[33]

GROWING BODY OF EVIDENCE

There is growing evidence that nepafenac has activity against many forms of macular edema. Wolf and colleagues[38] recently published a retrospective study of 450 consecutive patients with CME and concluded that those treated with prednisolone alone had a higher incidence of CME than those treated with prednisolone plus nepafenac 0.1%, suggesting that nepafenac 0.1% has prophylactic activity against CME. Hariprasad and coauthors[39] described the successful treatment of 6 cases of acute and chronic CME with nevanac, three of which previously failed combination treatment with a steroid and a conventional NSAID. Additionally, recent presentations at scientific meetings have also presented evidence that nepafenac, ketorolac, and bromfenac effectively treats macular edema.[40]

Further evidence and large clinical trials will be helpful in establishing a standard for the use of NSAIDs in the treatment of CME. ■

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CME QUESTIONS

1. In vivo pharmacodynamic studies comparing nepafenac, ketorolac, and bromfenac have confirmed that:
a. nepafenac reached anterior chamber aqueous concentrations 3.6 times higher than ketorolac
b. ketorolac reached anterior chamber aqueous concentrations 5 times higher than nepafenac
c. nepafenac reached anterior chamber aqueous concentrations 8 times higher than bromfenac
d. both a and c

2. The use of ocular corticosteroids have been associated with the risk of:
a. cataracts
b. glaucoma
c. infection
d. all of the above

3. The efficacy of NSAIDs is correlated with:
a. their ability to increase prostaglandin release
b. their ability to reduce the production of prostaglandin
c. their ability to inhibit cycooxygenase
d. both b and c

4. A prodrug NSAID is believed to result in greater corneal permeability than the acidic structures in conventional NSAIDs.
a. true
b. false

5. A rabbit model showed that a single application of nepafenac resulted in significant bioactivity:
a. 5 hours later
b. 10 hours later
c. 8 hours later
d. 6 hours later

6. What percentage of patients will develop increased retinal thickness on OCT following uncomplicated phacoemulsification?
a. 30-40%
b. 10-15%
c. 25-30%
d. 20-30%

7. The majority of conversion of nepafenac to amfenac occurs:
a. in the cornea
b. in the iris/ciliary body
c. in the retina/choroid
d. both b and c

8. A retrospective study of 450 consecutive patients with CME concluded that:
a. those treated with prenisolone plus nepafenac had a higher incidence of CME than those treated with prenisolone plus ketorolac
b. those treated with prednisolone alone had a higher incidence of CME than those treated with prednisolone plus nepafenac
c. those treated with ketorolac alone had a higher incidence of CME than those treated with prednisolone
d. all of the above

9. Corticosteroids are effective against macular edema due to:
a. reduction of interleukin-5, interleukin-6, and interleukin-8
b. reduction of prostaglandins and interferon gamma
c. reduction of vascular endothelial growth factor and tumor necrosis factor alpha
d. all of the above

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