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Cataract & Refractive Surgery TODAY

March 2006

Ocular NSAIDs: A New Option

Evaluating performance parameters to optimize therapy.

- **Potency and Penetration**
- **Efficacy**
- **Safety**
- **Clinical Experience to Date**

This continuing medical education activity is supported by an unrestricted educational grant from ISTA Pharmaceuticals, Inc.

Jointly sponsored by The Dulaney Foundation and *Cataract & Refractive Surgery Today*.

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STATEMENT OF NEED

Topical nonsteroidal anti-inflammatory drugs (NSAIDs) offer several benefits after refractive and cataract surgery. These agents can reduce patients' discomfort both during and after refractive procedures and reduce ocular inflammation, particularly in the cornea and conjunctiva. NSAIDs also lessen patients' discomfort during cataract surgery, an important benefit when the ophthalmologist uses topical anesthesia. Furthermore, by helping to maintain pupillary dilation during the cataract procedure, these drugs can lower the rate of complications. NSAIDs control inflammation in the first few postoperative days, and they inhibit the development of cystoid macular edema (CME), which can occur 4 to 6 weeks after cataract surgery.

The introduction of a new topical NSAID, bromfenac ophthalmic solution 0.09%, offers the ophthalmologist an additional clinical choice. This activity explores the utility of this agent and its unique properties, through available data and clinical experience, to facilitate therapeutic decision-making.

TARGET AUDIENCE

This activity is designed for ophthalmologists.

LEARNING OBJECTIVES

After the successful completion of this program, the participant should be able to:

- List the therapeutic applications of topical NSAIDs in ophthalmology and optimal performance characteristics in each of these applications
- Describe the relevance of IC_{50} potency assays and in vitro tissue penetration data to NSAID performance and selection
- Compare NSAID clinical trial designs and study protocols
- Evaluate NSAIDs' efficacy claims
- Describe available efficacy and safety data on bromfenac
- List barriers to patient compliance with NSAID therapy
- Incorporate the first b.i.d. NSAID into clinical protocols

METHOD OF INSTRUCTION

Participants should read the learning objectives and monograph in their entirety. After reviewing the material, they must complete the self-assessment test, which consists of a series of multiple-choice questions.

Upon completing this activity as designed and achieving a passing score of 70% or higher on the self-assessment test, participants will receive a CME credit letter awarding AMA/PRA category 1 credit 4 weeks after the registration and evaluation materials are received.

The estimated time to complete this activity as designed is 1 hour.

ACCREDITATION

This activity has been planned and implemented in accordance with essentials and standards of the Accreditation Council for Continuing Medical Education (ACCME) through the joint sponsorship of The Dulaney Foundation and *Cataract & Refractive Surgery Today*. The Dulaney Foundation is accredited by the ACCME to provide continuing medical education for physicians.

The Dulaney Foundation designates this educational activity for a maximum of one category 1 credit toward the AMA Physician's Recognition Award. Each physician should claim only those credits that he/she actually spent on the activity.

This activity was reviewed for relevance, accuracy of content, balance of presentation, and time required for participation by William Trattler, MD; Terry Kim, MD; and Y. Ralph Chu, MD.

DISCLOSURE

In accordance with the disclosure policies of The Dulaney Foundation and to comply with ACCME guidelines, all program faculty are required to disclose to the activity participants: (1) the existence of any financial interest or other relationships with the manufacturers of any commercial products/devices, or providers of commercial services, that relate to the content of their presentation/material, or the commercial contributors of presentation/material, or the commercial contributors of this activity, that could be perceived as a real or apparent conflict of interest; and (2) the identification of a commercial product/device that is unlabeled for use or an investigational use of a product/device not yet approved.

FACULTY DISCLOSURE DECLARATION

The physician faculty whose material appears in this program has a financial interest, relationship, or affiliation in the following forms:

Monte S. Dirks, MD, is a paid clinical researcher for ISTA Pharmaceuticals, Inc. He also receives research support and travel expenses from the company and is a member of the speaker's bureau for ISTA Pharmaceuticals, Inc.

Eric D. Donnenfeld, MD, is a consultant for ISTA Pharmaceuticals, Inc., and was an investigator in the phase 3 bromfenac clinical trials. Dr. Donnenfeld is a paid consultant for Allergan, Inc., and Alcon Laboratories, Inc.

Francis S. Mah, MD, is a paid consultant, and a member of the speaker's bureau for Allergan, Inc., Advanced Medical Optics, Inc., and ISTA Pharmaceuticals, Inc.

Barry A. Schechter, MD, is a consultant for ISTA Pharmaceuticals, Inc. He also receives research support and travel expenses from the company and is a member of the speaker's bureau for ISTA Pharmaceuticals, Inc. Dr. Schechter has received unrestricted grant support from Allergan, Inc., for clinical research.

MEET THE FACULTY

Monte S. Dirks, MD, is in private practice at the Black Hills Regional Eye Institute in Rapid City, South Dakota, and is an Associate Clinical Professor of Ophthalmology at the University of South Dakota. He may be reached at (605) 341-2000; dirks1@aol.com.

Eric D. Donnenfeld, MD, is a partner in Ophthalmic Consultants of Long Island and is Co-Chairman of Corneal and External Disease at the Manhattan Eye, Ear and Throat Hospital in New York. Dr. Donnenfeld may be reached at (516) 766-2519; eddoph@aol.com.

Francis S. Mah, MD, is Assistant Professor in the Department of Ophthalmology and Co-Medical Director of the Charles T. Campbell Ophthalmic Microbiology Laboratory at the University of Pittsburgh School of Medicine in Pennsylvania. Dr. Mah may be reached at (412) 647-2200; mahfs@upmc.edu.

Barry A. Schechter, MD, is Director of the Department of Cornea and External Diseases at the Florida Eye Microsurgical Institute in Boynton Beach. Dr. Schechter may be reached at (561) 737-5500; barrys_@hotmail.com.

A NEW NSAID

The applications of ocular nonsteroidal anti-inflammatory drugs (NSAIDs) have expanded during the past few years to include the treatment of postoperative pain, ocular inflammation, and photophobia in patients undergoing intraocular and refractive surgery. Additionally, these agents are useful against intraoperative miosis. The recent introduction of bromfenac ophthalmic solution 0.09% offers clinicians another therapeutic option in the NSAID class. Although in the absence of well-controlled head-to-head clinical trials it is difficult to make direct efficacy comparisons between NSAIDs, published data on differences in penetration and potency, dosing schedule (b.i.d. vs. t.i.d. vs. q.i.d.), onset or duration of activity, and tolerability become useful in selecting among these agents.

CONTENTS

The Importance of Potency and Penetration

Data available on the comparative potency and tissue penetration of available NSAIDs and the potential relevance of these differences for dosing and clinical performance is discussed.

All nonsteroidal anti-inflammatory drugs (NSAIDs) act by inhibiting cyclooxygenases, key enzymes responsible for the production of prostaglandins in arachidonic acid metabolism.

Cyclooxygenase-1 (COX-1) is expressed constitutively in almost all tissues, particularly the GI tract, platelets, endothelial cells, and kidneys. It appears to be responsible for the production of prostaglandins that maintain homeostatic functions, such as the integrity of the GI mucosa, platelet function, and the regulation of renal blood flow. Nonselective inhibition of COX-1 by systemic NSAIDs has been implicated in GI-toxicity.

Cyclooxygenase-2 (COX-2) expression, on the other hand, is an inducible mediator of prostaglandin production, and increases dramatically during inflammation and carcinogenesis. Inhibition of COX-2 results in beneficial anti-inflammatory, pain, and analgesic affects.

The degree to which the available NSAIDs inhibit either COX-1 or COX-2 differs. The relative potency of an agent against these mediators is measured by IC_{50}, the drug concentration required to inhibit enzyme activity by 50%. The lower the IC_{50}, the more potent is the molecule against the enzyme.

Although in vitro data on IC_{50} values are highly variable between laboratories and type of assay used, they provide some basis for evaluating relative potency. The focus is on the COX-2 enzyme, as this is the enzyme responsible for the mediation of pain and inflammation.

According to available data, it took 3.7 times less bromfenac than diclofenac, and 6.5 times less bromfenac than amfenac to inhibit the COX-2 enzyme (Figure 1).[1-3]

In summary, bromfenac is a more powerful inhibitor of COX-2 than either diclofenac or nepafenac, and therefore more potent than either diclofenac or nepafenac.

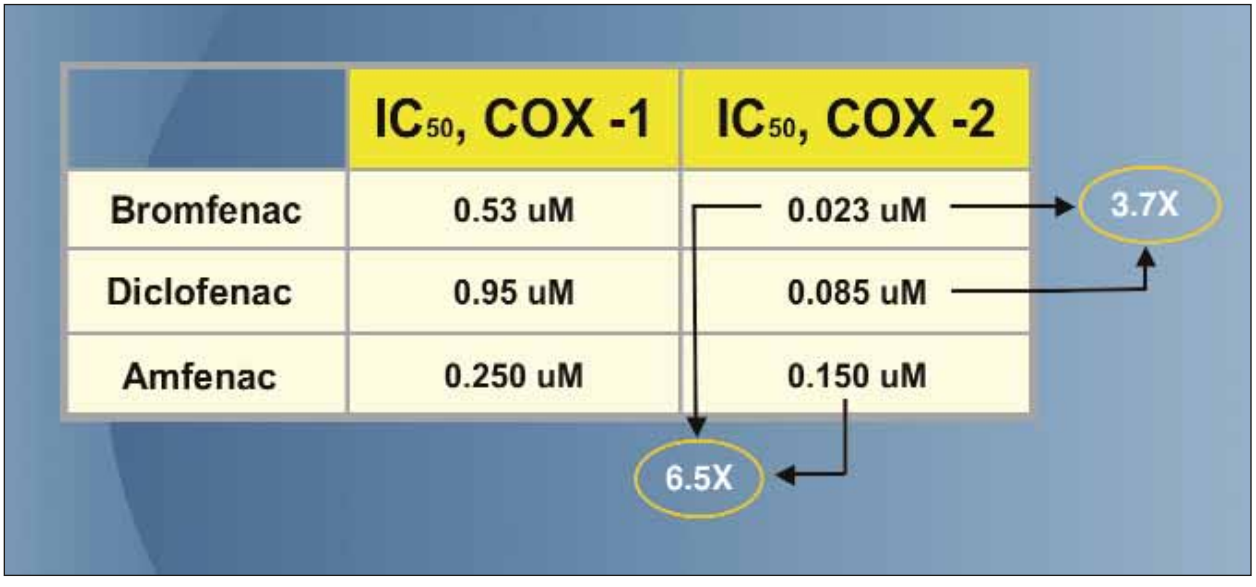

Figure 1. In terms of ocular NSAID potency against the COX-2 enzyme, bromfenac is 3.7 and 6.5 times more potent than diclofenac and amfenac, respectively.

CHARACTERISTICS OF NSAIDs

By Francis Mah, MD

Ocular nonsteroidal anti-inflammatory drugs (NSAIDs) are used to manage the pain associated with refractive surgery, because this group of drugs has analgesic and sometimes mild anesthetic properties. NSAIDs are used after cataract surgery and other intraocular procedures to alleviate postoperative inflammation.

For each application, it is essential that the NSAID reach target tissues efficiently and remain in effective concentrations over a sufficient period of time. Based on in vitro assays, it is clear that there are differences in these parameters between NSAIDs, and these differences may provide a guide for therapeutic decision making. Indeed, just as improvements in penetration and potency differentiated the fourth-generation fluoroquinolone antibiotics from their predecessors, the evolution of NSAIDs will be similar. It is apparent that it is the combination of potency and therapeutic penetration that will define clinical efficacy and lack of toxicity. *Potency* describes the strength of the activity and, therefore, affects the duration of activity in the NSAID class, which determines dosing. Without appropriate penetration of the drug, not all of the therapeutic benefits will be achieved. Although topical applications and surface activity is required (eg, in refractive surgery), NSAIDs also need to penetrate into the eye to protect and treat postoperative inflammation and possible cystoid macular edema (CME). Only with both qualities will the drug be useful to clinicians.

In cataract surgery, an NSAID needs to penetrate the ocular tissues from the anterior chamber to the ciliary body and to the iris in order to strengthen the blood-aqueous barrier and prevent the release of proteins and pro-inflammatory mediators.

Refractive surgeons use NSAIDs to manage the pain of ocular surface tissues, primarily after PRK. They also administer the agents in the eyes of post-LASIK patients to make them more comfortable. In terms of NSAIDs' penetration requirements for refractive surgery, they only need to infiltrate the cornea. It can be helpful to have some of the drug in the anterior chamber, but the drugs' entering the cornea is sufficient for use after refractive surgery.

Furthermore, the anti-inflammatory properties of NSAIDs provide protection against postoperative CME after cataract surgery. The vascular instability of CME lies within the retina and the choroid. Therefore, and most importantly, NSAIDs need to reach the back of the eye for the treatment and/or prophylaxis of CME.

CME has been reported to be the most common cause of decreased vision following uncomplicated cataract surgery. In one study[1] utilizing the sensitive OCT technology to measure retinal thickness, 12% of routine, uncomplicated phacoemulsification resulted in CME. In that same study, the use of topical NSAIDs before and after the surgery resulted in zero cases of CME. As our surgical technology, skills, and outcomes improve, our patients are becoming more and more demanding. Patients are no longer happy with anything short of 20/20 vision, let alone other unmentionable complications, such as endophthalmitis. NSAIDs have been proven to treat CME, so it makes perfect sense that an NSAID that penetrates into the vitreous cavity and reaches the retina and choroid at high concentrations will prevent CME better than an NSAID that does not have the same properties.

The optimal NSAID has a rapid delivery into targeted tissues but preferably all ocular tissues starting from the front and continuing to the back of the eye. Additionally, the longer the active levels of an NSAID are maintained in the target tissues, the more favorable the situation is for the patient in terms of his adherence to therapy because the frequency of dosing is lower.

Bromfenac is a b.i.d. medication that controls pain to the same degree as the NSAIDs that are dosed q.i.d. and t.i.d. Due to bromfenac's potency as well as its ability to penetrate the anterior chamber and the vitreous cavity, twice-daily dosing is sufficient and should reduce the likelihood of cytotoxic effects while improving patients' compliance.

1. McColgin AZ, Raizman MB. Efficacy of topical Voltaren in reducing the incidence of postoperative cystoid macular edema. *Invest Ophthamol Vis Sci*. 1999;40:S289.

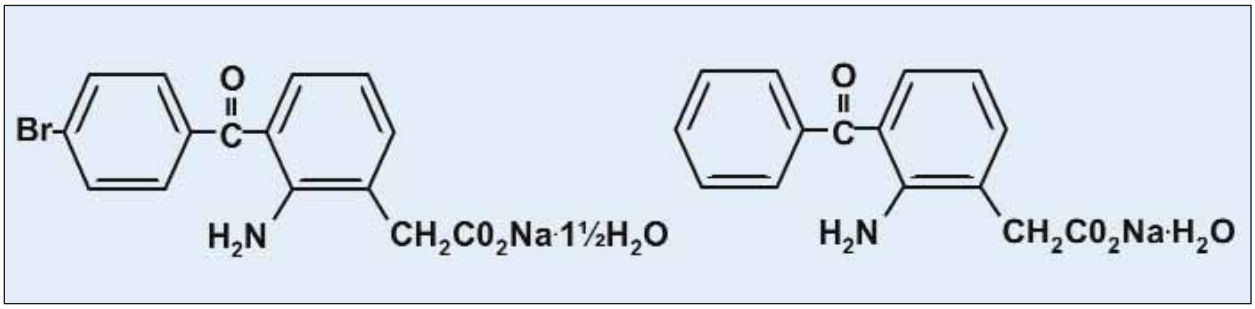

Figure 2. The bromfenac molecule (left) is similar to the amfenac molecule (right).

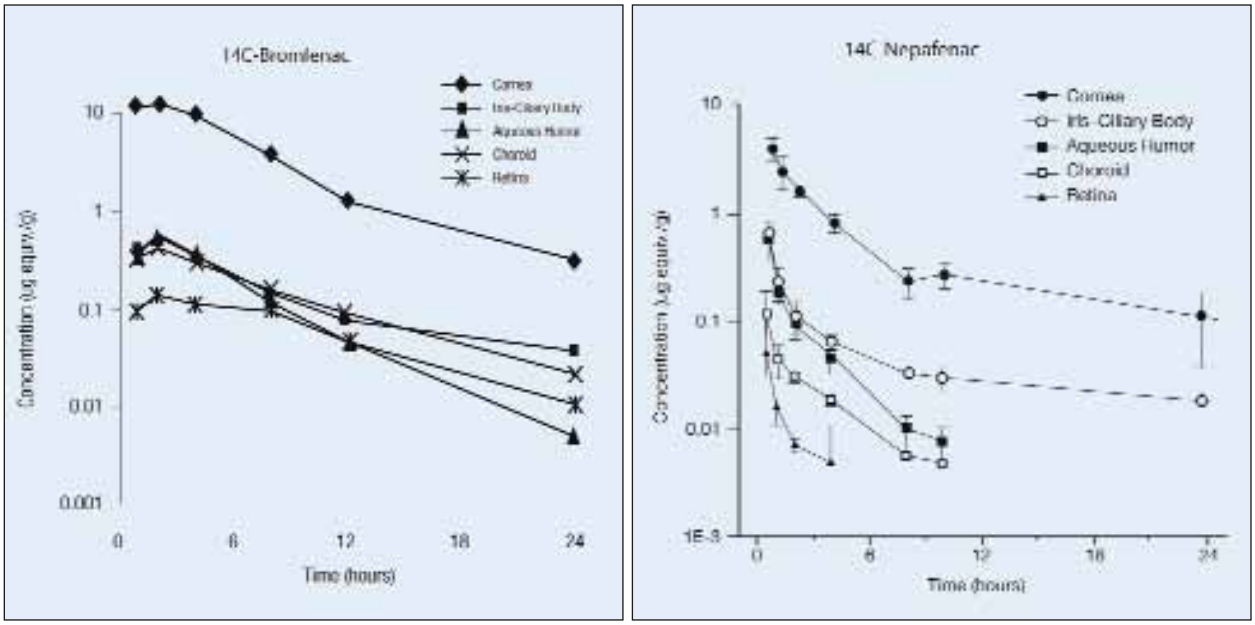

Figure 3. Ocular concentrations of bromfenac were detectable for the longest time period in comparison to nepafenac.

TISSUE PENETRATION

The chemical structure of bromfenac is identical to that of amfenac except for the addition of a bromine moiety at position 4 (Figure 2), which increases the lipophilicity of the molecule.[4] As a result, one could expect increased penetration and uptake of bromfenac into ocular tissues. This was demonstrated in a pharmacokinetic study in which a single drop of radiolabeled bromfenac (mean 0.29mg/drop) was administered to rabbits. Bromfenac was detectable in all ocular tissues over a 24-hour period. The highest concentrations detected were in the cornea, followed respectively by the iris and ciliary body, choroid, retina, and aqueous humor.[5]

A similar study using a single drop of 0.3% amfenac demonstrated ocular penetration as well.[6] The results and relative ocular concentrations of these two trials are depicted in Figure 3. The clinical importance of enhanced penetration remains to be demonstrated. However, the enhanced potency of bromfenac allows for b.i.d. dosing and may account for the earlier efficacy (post-surgical day 2) seen in the reduction of pain and inflammation in clinical trials.

1.. Data on file at ISTA Pharmaceuticals, Inc.

2. Gamache DA, Graff G, Brady MT, et al. Nepafenac, a unique nonsteroidal prodrug with potential utility in the treatment of trauma-induced ocular inflammation: I. 3. Jett MF, Ramesha CS, Brown CD, et al. Characterization of the analgesic and anti-inflammatory activities of ketorolac and its enantiomers in the rat. *J Pharmacol Exp Ther.* 1999;288:1288-1297.

4. Walsh DA, Moran HW, Shamblee DA, et al. Anti-inflammatory agents. 3. Synthesis and pharmacological evaluation of 2-amino-3benzoylphenylacetic acid and analogues. *J Med Chem.* 1984;11:1379-1388.

5. Data on file at ISTA Pharmaceuticals, Inc.

6. Hellberg MR, Nixon JC. Use of non-steroidal anti-inflammatory agents in combination with compounds that have PF prostaglandin agonist activity to treat glaucoma and ocular hypertension. Alcon Laboratories, Inc., assignee. U.S. Patent 6,342,524 B1. Jan. 29, 2002.

Efficacy

A review of the study design and results for the bromfenac phase 3 trials is presented.

APPROVALS

Bromfenac was approved in Japan in May 2000 under the trade name Bronuck for the treatment of blepharitis, conjunctivitis, scleritis, and postoperative inflammation. To date, more than 6 million patients have been treated with bromfenac in that country. The FDA approved the same formulation that was approved and used in Japan in March 2005 as the first nonsteroidal anti-inflammatory drug (NSAID) dosed b.i.d. for the treatment of ocular inflammation following cataract surgery. In January 2006, the FDA granted an expanded indication for bromfenac for the treatment of pain following cataract surgery.[1]

PHASE 3 TRIALS

Two US phase 3 clinical trials of bromfenac were completed, both of which demonstrated the drug's efficacy. A total of 527 patients were enrolled in the randomized, double-masked, placebo-controlled clinical trials, of which 356 received bromfenac and 171 received placebo. Patients enrolled in these trials had to have had undergone cataract surgery and had a Summed Ocular Inflammation Index Score (SOIS) of 3.7 out of 4 on day 1 postoperatively, with no presurgical dosing of an NSAID. Patients did not receive any anti-inflammatory agents until 1 day after surgery (after the inflammation had occurred). Patients then instilled bromfenac b.i.d. for 14 days. The endpoints measured included the reduction in summed cell and flare scores, a decrease in anterior chamber cell score, a reduction in anterior flare score, and a resolution of pain. Efficacy was measured by comparing the proportion of bromfenac versus placebo patients who achieved a SOIS of zero at days 3, 8, and 15, postoperatively (Figure 4).[2]

At each post-treatment visit, for all efficacy measurements, the effect of bromfenac was statistically signifi-

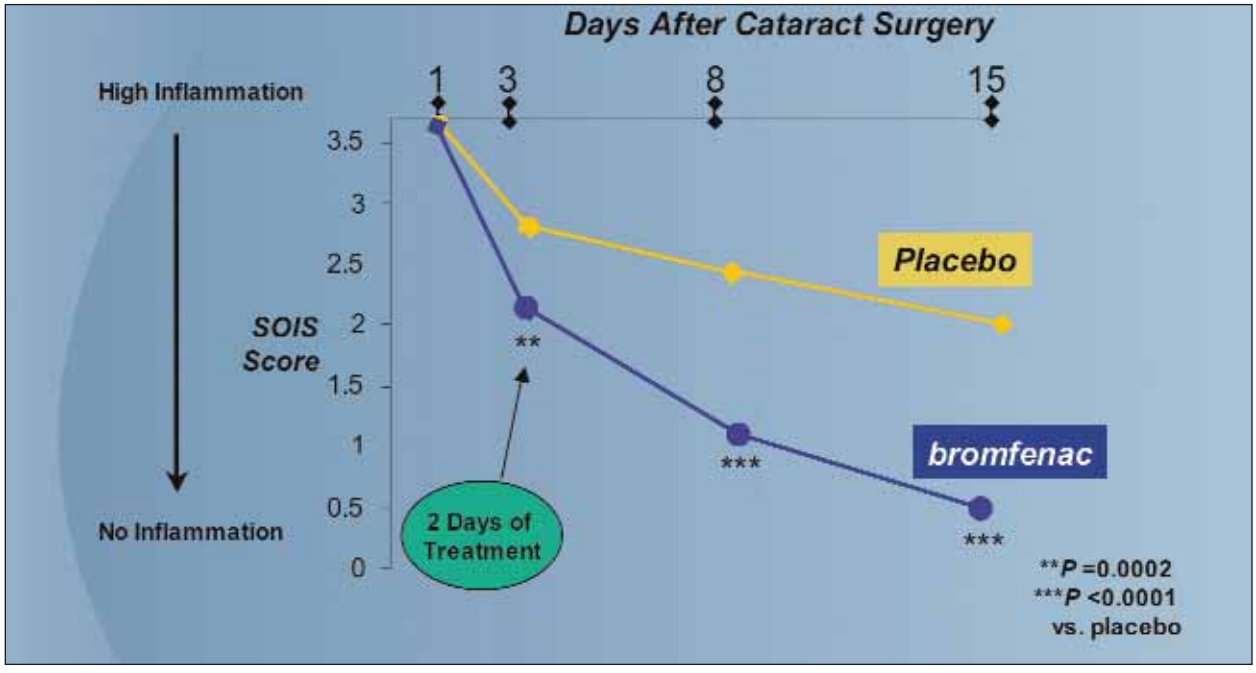

Figure 4. Bromfenac achieved statistical significance on the first treatment evaluation (2 treatment days) and achieved statistically significant reduction from baseline at all study visits for the treatment of inflammation.

EVALUATING NSAIDs' CLINICAL EFFICACY

By Barry A. Schechter, MD

When reviewing nonsteroidal anti-inflammatory drugs' (NSAIDs) efficacy data, one needs to consider such factors as predosing and the management of inflammation and pain postoperatively. The best way to compare the effectiveness of the different agents is to conduct head-to-head clinical studies. Unfortunately, none has been published thus far. Therefore, we have to compare the clinical trials of the available NSAIDs and extrapolate as to how efficacious the medications are by analyzing the different variables. One approach is to compare drugs' affinities for the cyclooxygenase-2 (COX-2) enzyme, the major enzyme that produces prostaglandins that promote inflammation and pain. According to Fitzgerald et al[1] and Gamache et al,[2] bromfenac has a great affinity for COX-2 as far as the IC_{50}, at which the enzyme activity is inhibited by 50%, which is several log units more than diclofenac and amfenac. This stronger affinity allows for only b.i.d. dosing.

The phase 3 clinical trials for bromfenac 0.09% were quite stringent. There was no predosing of medication in patients who were to undergo cataract surgery, and, in order for patients to be entered into the clinical trial, the postoperative eye had to be very inflamed (degree of cell and flare averaging 3.7 out of a possible 4). Results of the phase 3 clinical trials showed that after only 4 drops of bromfenac (2 days of therapy), there was already a statistically significant reduction in the amount of cell and flare in the anterior chamber. The similarly designed phase 3 trial for ketorolac showed that 7 days (28 drops) were needed to statistically reduce flare and required 14 days (56 drops) to show a statistically significant reduction in anterior chamber cells.[3] In the phase 3 clinical trial for nepafenac in which patients were predosed with the drug t.i.d., starting the day before surgery, statistical significance in reduction of cells and flare was noted on day 16 (48 drops).[4]

The control of postoperative pain was assessed as a secondary endpoint. After 3 days of bromfenac treatment (4 drops), clinical significance versus placebo was achieved with 87.6% of bromfenac patients pain free. By 8 days (14-16 drops) of bromfenac treatment, clinical significance versus placebo was achieved with 93.3% of bromfenac patients pain free. On postoperative day 6 (24 drops), ketorolac first achieved statistical significance versus placebo. After 14 days of treatment with nepafenac (42 drops), approximately 95% of patients were pain free, however, nepafenac patients were predosed and treated immediately following surgery..

Only 3.1% of patients receiving bromfenac were dismissed from the phase 3 clinical trials due to lack of inflammation control, compared with 28% of ketorolac patients in the ketorolac phase 3 trial[5] and 10% for the nepafenac phase 3 trial.[6]

Due to its analgesic properties, strong anti-inflammatory potential, and efficient tissue penetration, I have found bromfenac to be a versatile addition to my NSAID armamentarium. I have used bromfenac off label to treat nonsurgical iritis, peripheral inflammatory keratitis, *Staphylococcus* hypersensitivity reactions, and corneal abrasions. Furthermore, I have used it in patients with chemical keratoconjunctivitis and filamentary keratitis. When treating dry eye in conjunction with topical cyclosporine, my patients prefer bromfenac to ketorolac, which I had previously utilized, because there is less stinging.[7]

NSAIDs allow patients with corneal abrasions to recuperate comfortably and return to work quickly. Previously, the standard treatment involved administering an antibiotic ointment, patching a patient's eye, and oftentimes oral opiates to control pain.

Additionally, bromfenac is very helpful in patients who undergo refractive surgery; ie, LASIK, surface ablation, or limbal relaxing incisions. Bromfenac has been helpful after pterygium surgery with conjunctival grafting. Patients have not suffered significant pain, and there have been no problems with wound healing—the NSAID is discontinued once the epithelium has healed. Bromfenac only needs to be used b.i.d., because it has potent inhibitory specificity for the COX-2 enzyme, which reduces the epithelial toxic effect of preservatives, which are present in nearly all commercially available topical NSAIDs.

1. FitzGerald GA, Patron C. The coxibs, selective inhibitors of cyclooxygenase-2. *N Engl J Med*. 2001;345:433-442.
2. Gamache DA, Graff G, Brady MT, et al. Nepafenac, a unique nonsteroidal prodrug with potential utility in the treatment of trauma-induced ocular inflammation: I. Assessment of anti-inflammatory efficacy. *Inflammation*. 2000;24:357-370.
3. Heier J, Cheetham JK, Degryse R, et al. Ketorolac tromethamine 0.5% ophthalmic solution in the treatment of moderate to severe ocular inflammation after cataract surgery: a randomized, vehicle-controlled clinical trial. *Am J Ophthalmol*. 1999;127:253-259.
4. Data on file at Alcon Laboratories, Inc.
5. Acular LS [package insert]. Irvine, CA: Allergan, Inc.
6. Personal communication with P. Cockrum, September 24, 2005.
7. Schechter BA. The evaluation of ketorolac (Acular LS) to improve patient comfort during the induction phase of cyclosporine A (Restasis ophthalmic emulsion) therapy. *J Ocular Pharmacol Ther. In press.*

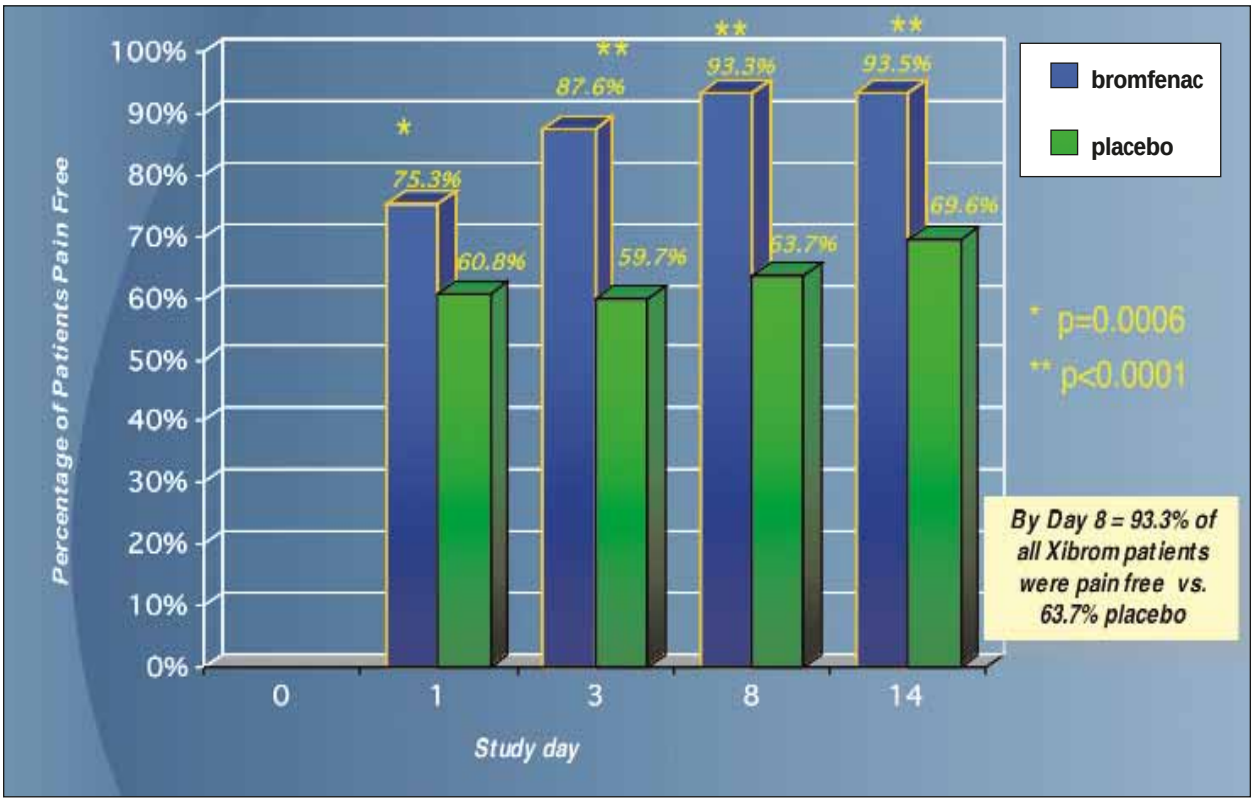

Figure 5. The resolution of pain after cataract surgery was rapid in patients that received bromfenac therapy.

cant when compared with the effect of placebo. After 2 days of treatment with bromfenac, patients achieved a significant drop in their SOIS to less than 2 ($P \leq .0002$), which dropped to less than 1 on day 7 of treatment ($P \leq .0001$) and less than 0.5 on day 14 of treatment ($P \leq .0001$).[2]

On treatment day 3, 8% of the bromfenac patients compared with 1% of placebo patients achieved a SOIS of zero. Eighty-one percent of the bromfenac patients achieved improvements in inflammation on or before postoperative day 15 versus less than 52% of the patients who received placebo.[2]

An additional efficacy endpoint was the time required for the resolution of ocular pain in patients who reported pain following cataract surgery (20% of subjects in the trials). The bromfenac group demonstrated a statistically significant difference in median time to resolution of ocular pain of 2 days, compared with 5 days for patients receiving the vehicle. Furthermore, 87.6% ($P<.0001$) of all patients treated with bromfenac were pain-free within 3 days of being treated with bromfenac b.i.d. (approximately 4 to 6 doses). By treatment day 8 (14 to 16 doses) 93.3% of these patients were pain-free versus 63.7% ($P<.0001$) of patients treated with vehicle during that period (Figure 5).[3]

DOSING

Bromfenac is the first NSAID to be approved for b.i.d. dosing. In contrast, approved dosing for nepafenac ophthalmic suspension and ketorolac tromethamine ophthalmic solution is one drop t.i.d. and one drop q.i.d., respectively.[4-6] According to a study by Ikeda et al,[7] which evaluated factors influencing patients' use of ophthalmic solutions, patients who administered ophthalmic solutions once or twice daily were more compliant than those in other patient groups. Other factors influencing patients' adherence to prescribed therapy were the number of ophthalmic solutions, patients' age, taste of the drug, administration intervals, number of drops used, and hand washing before the application of ophthalmic solutions.

1. Data on file at ISTA Pharmaceuticals, Inc.
2. Donnenfeld ED, Holland EJ, Stewart R, Grillone LR, for the Bromfenac Study Group. Topical Xibrom 0.1%, an investigational NSAID for post-cataract surgery inflammation, markedly decreases inflammation. Paper presented at: The Annual ASCRS. April 15, 2005, Washington, DC.
3. Donnenfeld ED, Holland EJ, Stewart R, et al. Topical Xibrom 0.1%, an investigational NSAID, significantly and rapidly decreased post-cataract surgery inflammation and reduced ocular pain. *Invest Ophthalmol Vis Sci.* 2005;46:E-abstract 791.
4. Xibrom [package insert]. Irvine CA: ISTA Pharmaceuticals, Inc.
5. Data on file at Alcon Laboratories, Inc.
6. Acular LS [package insert]. Irvine, CA: Allergan, Inc.
7. Ikeda H, Sato M, Tsukamoto H, et al. Evaluation and multivariate statistical analysis of factors influencing patient adherence to ophthalmic solutions. *Yakugaku Zasshi.* 2001;121:799-806.

Safety

Clinical trial and postmarketing surveillance data on bromfenac is assessed.

In US phase 3 trials, the incidence rate of common treatment-emergent ocular adverse events associated with bromfenac was ≤ 2% of 356 patients. The incidence of burning and stinging in bromfenac patients was only 1.4%, and the incidence of cystoid macular edema was 1.4%.[1] In this same trial, four patients discontinued using bromfenac due to adverse ocular events, including iritis, lid edema, and cystoid macular edema, all of which were possibly related to bromfenac. Bromfenac is contraindicated in patients with known hypersensitivity to any ingredient in the formulation, and most commonly reported adverse experiences include abnormal sensation in the eye; conjunctival hyperemia; ocular irritation, pain, pruritus, and redness; headache, and iritis. These events were reported in 2% to 7% of patients.[2]

As part of bromfenac's US New Drug Application, postmarketing information was submitted to the FDA from Senju Pharmaceuticals Inc. Ltd. (Osaka, Japan [bromfenac was developed by Senju Pharmaceuticals Inc. Ltd.]). The postmarketing surveillance survey included data from 2.7 million patients who had used bromfenac 0.09% in Japan between 2000 and 2004 for a wide variety of indications and treatment periods.[1] Since bromfenac's initial marketing in Japan beginning in July 2000 to date, the drug has been used in more than 6 million patients, and there has been no reported case of serious systemic adverse events and only 14 cases of serious ocular adverse events (including three corneal erosions, three corneal perforations, four corneal ulcers, three conjunctival disorders, and one epithelial defect), an event rate of 0.00023%.[1-3] Three of the previously reported cases—one corneal erosion in 2001, and two corneal erosions in 2002—were recently described in the literature.[4] Each of these cases resolved with conservative treatment.

1. Data on file at ISTA Pharmaceuticals, Inc.
2. Congdon NG, Schein OD, von Kulajta P, et al. Corneal complications associated with topical ophthalmic use of nonsteroidal anti-inflammatory drugs. *J Cataract Refract Surg.* 2001;27:622-631.
3. Guidera AC, Luchs JI, Udell IJ. Keratitis, ulceration, and perforation associated with topical nonsteroidal anti-inflammatory drugs. *Ophthalmology.* 2001;108:936-944.
4. Asai T, Nakagami T, Mochizuki M, et al. Three cases of corneal melting after instillation of a new nonsteroidal anti-inflammatory drug. *Cornea.* 2006;25:224-227.

DATA CONFIRM BROMFENAC'S SAFETY

By Monte S. Dirks, MD

Although bromfenac 0.09% is a new agent for US ophthalmologists, we have an unusually large body of information confirming its safety, including rigorous phase 3 clinical trials[1] and extensive postmarketing data from Japan.[2]

Two US phase 3 clinical trials assessed the incidence of ocular effects with the use of bromfenac after cataract surgery. The results showed a minimal incidence of adverse events associated with bromfenac. The reported events were those expected following cataract surgery. Only 1.4% reported burning and stinging. Cystoid macular edema was reported in 1.4% of the bromfenac group compared with 4.7% of the placebo group. As an investigator in this study, I was impressed by the postoperative comfort reported by patients treated with bromfenac.[1]

The most noteworthy safety data from the clinician's standpoint relate to the Japanese studies and the Japanese Ministry of Health's surveillance data. Despite genetic differences, the sample size was very large and the data span nearly 5 years. Certainly, we know more about bromfenac than we do about nepafenac, which has only been used in the US, and ketorolac, for which I was an investigator and witnessed its full development. To date, I believe there is sufficient data from which one can determine which ocular nonsteroidal anti-inflammatory drug (NSAID) is safe and comfortable.

One of the major strengths of bromfenac is that it has one of the lowest incidence of burning and stinging upon instillation when compared with the other available ocular NSAIDs.[3-6] In refractive surgery, PRK patients in particular may benefit from bromfenac, because it is more comfortable in comparison with the sting/burn rate of ketorolac and nepafenac, which may add to these patients' postoperative discomfort. Dry eye and pterygium patients may also prefer bromfenac over conventional topical anti-inflammatories, which can cause significant irritation on their own. Bromfenac works very well in patients who already have some ocular irritation.

Last, bromfenac mitigates concerns about toxicity, because it is dosed b.i.d. as opposed to q.i.d. for ketorolac and t.i.d. for nepafenac. This less frequent-dosing also improves patient compliance.

1. Data on file, ISTA Pharmaceuticals, Inc.
2. Data on file, ISTA Pharmaceuticals, Inc.
3. Xibrom [package insert]. Irvine, CA: ISTA Pharmaceuticals, Inc.
4. Acular [package insert]. Irvine, CA: Allergan, Inc.
5. Nevanac [package insert]. Fort Worth, TX: Alcon Laboratories, Inc.
6. Voltaren [package insert]. East Hanover, NJ: Novartis Pharmaceuticals Corporation.

Clinical Experience to Date

An overview of clinical experience with bromfenac to date, focusing on evaluations of physician satisfaction and patient comfort.

POSTMARKETING STUDIES

US postmarking studies of bromfenac performed since its initial approval include examinations of the relative comfort of the drug upon instillation and its corneal anesthetic characteristics and physician satisfaction with a range of performance parameters.[1,2]

ASSESSMENT OF COMFORT AND CORNEAL ANESTHESIA

Twenty volunteers with normal, healthy eyes were enrolled in a US postmarketing study[1] that compared the comfort and corneal anesthetic properties of both bromfenac 0.09% and ketorolac 0.4%. Each subject was administered a single drop of drug in a random and masked fashion, and then they were asked to rate the severity of burning and stinging on a scale of 0 to 4. According to the study's results, 17 subjects (85%) reported no burning or stinging with bromfenac, compared with 7 subjects (35%) with ketorolac. None of the bromfenac subjects reported moderate or severe burning or stinging compared with 6 (30%) subjects who received ketorolac.[1]

PHYSICIAN SATISFACTION

An early experience study[2] performed in the US rated physicians' initial experience with the drug. In the trial, participants treated a minimum of 10 patients with bromfenac. Results included data from 225 ophthalmologists and 2,604 patients who received bromfenac. The ophthalmologists rated the performance of bromfenac in control of inflammation, ease of use by patients, patient compliance, comfort on instil-

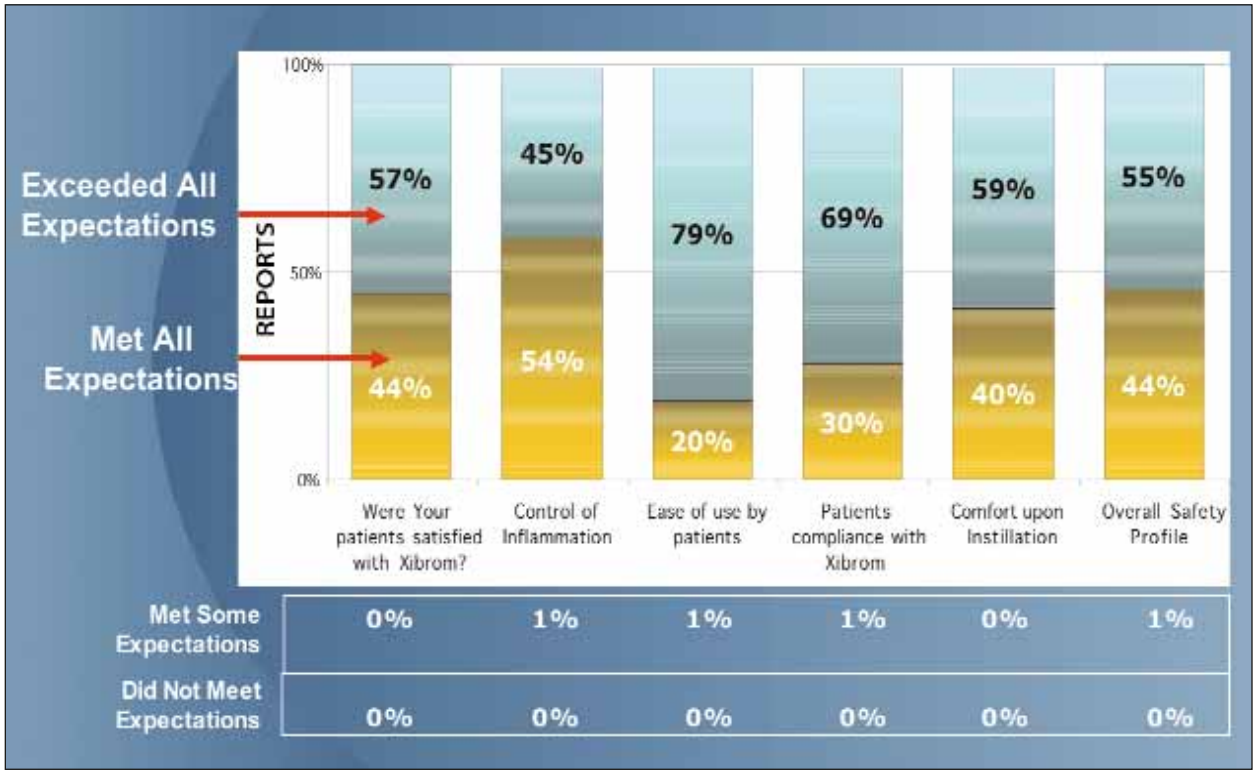

Figure 6. In an early experience study[2] of bromfenac, physicians' expectations of the drug's performance were either exceeded or met in 99% to 100% of reports.

lation, overall safety profile, and patient satisfaction, using four descriptors: (1) very satisfied (exceeded expectations); (2) satisfied (met expectations); (3) dissatisfied (met some expectations); and (4) very dissatisfied (did not meet expectations). According to the results of this study, ophthalmologists' expectations were exceeded or met in 99% to 100% of reports (Figure 6).

1. Perry HD, Chou TY. A comparison of Xibrom and Acular LS in a test of comfort and corneal anesthesia. Abstract pending acceptance at ARVO as of February 15, 2006.
2. Xibrom First Experience Trial 2005. Data on file, ISTA Pharmaceuticals, Inc.

PERSONAL EXPERIENCE WITH BROMFENAC

By Eric D. Donnenfeld, MD

To date, I have had a positive experience with bromfenac. The initial clinical trials established that this b.i.d. drug could reduce inflammation following cataract surgery. The medication has been well tolerated, and patient acceptance has been exceptional. Notably, the medication induces little burning or stinging and is the most comfortable nonsteroidal anti-inflammatory drug (NSAID) I have used. However, it is difficult to make meaningful efficacy comparisons with other NSAIDs in the absence of head-to-head studies.

One of the major concerns with any medication, and specifically with an NSAID, is the issue of corneal melts as was seen with generic diclofenac.[1] To date, I have not seen this problem with this medication, and bromfenac's track record in Japan, where it has been used for 5 years, suggests that it will be well tolerated. Continued experience in this market will confirm bromfenac's safety profile.

In comparing available agents, it is possible to say that patient comfort and its b.i.d. dosing are major advantages of bromfenac. Numerous studies[2] involving dosing schedules have shown that a b.i.d. schedule is much better tolerated than a q.i.d. one. Simply stated, patients will take their medications twice per day but are not nearly as compliant with four-times-per-day dosing. Bromfenac's minimal burning and stinging is also a contributing feature for better patient compliance, because previous experience has shown that medications with side effects are not used as directed.

NSAIDs in general are a potent addition to the anti-inflammatory armamentarium following ophthalmic procedures. When they are used in conjunction with a topical corticosteroid, there is a synergy that dramatically increases onset of action and efficacy. Such a combination hastens the return of visual acuity and reduces the incidence of intraocular inflammation. Although the prevention of cystoid macula edema (CME) is one of the most important indications for a topical NSAID, the combination therapy more rapidly resolves CME.[3]

In conclusion, NSAIDs have become an integral part of my surgical armamentarium. I use a topical NSAID for 3 days prior to any intraocular surgery and continue the agent for 3 weeks postoperatively. NSAIDs dramatically improve the patient's and surgeon's experience during cataract surgery by reducing pain, intraocular inflammation, and CME. Additionally, they maintain pupil size during cataract surgery and provide more rapid visual rehabilitation while not delaying wound healing like steroids can. I predict that NSAID use with cataract surgery will increase markedly as the efficacy of these medications is established and patient demand for painless, rapid visual rehabilitation postoperatively becomes the standard. The future for NSAIDs in ophthalmic surgery is bright with their safety and efficacy becoming established. Innovations include the possibility of intracameral usage in conjunction with topical therapy as well as even more potent and safer molecules in the future.

1. Guidera AC, Luchs JI, Udell IJ. Keratitis, ulceration, and perforation associated with topical nonsteroidal anti-inflammatory drugs. *Ophthalmology.* 2001;108:936-944.
2. Kosoko O, Quigley HA, Vitale S, et al. Risk factors for noncompliance with glaucoma follow-up visits in a residents' eye clinic. *Ophthalmology.* 1998;105:2105-2111.
3. Heier JS. Topping TM Baumann W, et al. Ketorolac versus prednisolone versus combination therapy in the treatment of acute pseudophakic cystoid macular edema. *Ophthalmology.* 2000;107:2034-2039.

CME QUESTIONS

Circle the most appropriate answer in the "ANSWER SECTION" on the following page.

1. Which of the following are therapeutic applications for the topical NSAIDs described in the literature?
a. treatment of postoperative pain
b. treatment of postoperative inflammation
c. prevention of cystoid macular edema
d. all of the above

2. Inhibition of which cyclooxygenase enzyme reduces ocular inflammation and pain?
a. COX-1
b. COX-2

3. Which characteristics of topical NSAIDs can be enhanced to improve their clinical performance?
a. tissue penetration
b. potency
c. COX selectivity
d. all of the above

4. In assessing relative potency of NSAIDs using in vitro assays, which statement is true?
a. the higher the IC_{50} value, the greater the relative potency
b. the lower the IC_{50} value, the greater the relative potency

5. A single drop of bromfenac produced measurable tissue levels in the cornea, iris, ciliary body, choroid, aqueous humor, and retina for 24 hours.
a. true
b. false

6. Which of the following parameters vary between NSAID clinical trials?
a. whether NSAID dosing prior to surgery was allowed
b. if and at what point concomitant steroid use was allowed
c. the degree of inflammation or pain at treatment initiation
d. at what time point, postoperatively, treatment was initiated
e. all of the above

7. In clinical trials, at which time point was the reduction of inflammation produced by b.i.d. bromfenac statistically significant over placebo?
a. day 3
b. day 8
c. day 15
d. all time points

8. More than 87% of patients reporting ocular pain who were treated with bromfenac in clinical trials were pain free within:
a. 3 days
b. 5 day
c. 8 days
d. 15 days

9. Research suggests that dosing of ophthalmic medications once or twice per day improves compliance.
a. true
b. false

10. Which statement about safety and tolerability is associated with bromfenac?
a. the rate of burning and stinging upon instillation in US clinical trials was less than 1.4%
b. the rate of serious ocular adverse events in Japanese post-marketing surveillance studies was 0.00023%
c. no serious systemic adverse events have been reported in Japan after more than 5 years and 6 million patient uses
d. all of the above

REGISTRATION/EVALUATION FORM

To obtain AMA/PRA category 1 credit, you must:

- Read the learning objectives and the monograph and complete the self-assessment test.
- Complete this registration/evaluation form and record your test answers in the Answer Section below.
- Send the Registration/Evaluation form to **The Dulaney Foundation, Post Office Box 25271, Tampa, FL 33622-5271, or fax to (813) 258-8002.**
- Retain a copy of your test answers. Your answer sheet will be graded, and if you achieve a passing score of 70% or better, you will receive a CME credit letter awarding AMA/PRA category 1 credit by mail within 4 weeks. If you do not achieve a passing score, you will be notified and offered the opportunity to complete the activity again.

ANSWER SECTION

Circle the best answer for each question on page 13.

1. A B C D	2. A B	3. A B C D	4. A B	5. A B
6. A B C D E	7. A B C D	8. A B C D	9. A B	10. A B C D

REGISTRATION FORM

First name _____ Last name _____ Degree (MD, PhD) _____

Position _____ Specialty _____

Institution or practice name _____

Address _____

City _____ State _____ Zip Code _____ Country _____

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The processing fee has been underwritten by an unrestricted educational grant from ISTA Pharmaceuticals, Inc.

I attest that I have completed this activity as designed and I am claiming ____ (up to 1 credit) AMA/PRA category 1 credit.

Signature _____ Date _____

Credit for this activity is available until March 31, 2007.

The planning and execution of useful and educationally sound continuing education activities are guided in large part by input from participants. Please assist us in evaluating the effectiveness of this activity and make recommendations for future educational offerings by completing this evaluation form. Your response will help ensure that future programs are informative and meet the educational needs of all participants. Please note: CME credit letters and long-term credit retention information will only be issued upon receipt of this completed evaluation. Thank you for your cooperation!

OBJECTIVES

After successful completion of this program, you should be able to:

	Strongly Agree				Strongly Disagree
• List the therapeutic applications of topical NSAIDs in ophthalmology and optimal performance characteristics in each of these applications	5	4	3	2	1
• Describe the relevance of IC_{50} potency assays and in vitro tissue penetration data to NSAID performance and selection	5	4	3	2	1
• List the goals of therapeutic intervention for dry eye disease	5	4	3	2	1
• Compare NSAID clinical trial designs and study protocols	5	4	3	2	1
• Evaluate NSAIDs' efficacy claims	5	4	3	2	1
• List barriers to patient compliance with NSAID therapy	5	4	3	2	1
• Incorporate the first b.i.d. NSAID into clinical protocols	5	4	3	2	1

OVERALL EVALUATION

• The information presented increased my awareness/understanding of the subject	5	4	3	2	1
• The information presented will influence how I practice	5	4	3	2	1
• The information presented will help me improve patient care	5	4	3	2	1
• The faculty demonstrated current knowledge of the subject	5	4	3	2	1
• The program was educationally sound and scientifically balanced	5	4	3	2	1
• The program avoided commercial bias or influence	5	4	3	2	1
• Overall, the program met my expectations	5	4	3	2	1
• I would recommend this program to my colleagues	5	4	3	2	1

- If you anticipate changing one or more aspects of your practice as a result of your participation in this activity, please provide a brief description of how you plan to do so: _____
- Please provide any additional comments pertaining to this activity (positive and negative) and suggestions for improvements: _____

_____

- Please list any topics you would like to see addressed in future educational activities: _____

_____