with similar topographic patterns within the context of penetrating keratoplasty. However, it should be emphasized that when screening patients for refractive surgery, there is limited need to differentiate between keratoconus suspects and pellucid suspects. The claw-shaped topographic pattern discussed by the authors should be interpreted as abnormal in all cases and should exclude patients from consideration for laser in situ keratomileusis.  

J. BRADLEY RANDLEMAN  
Atlanta, Georgia

REFERENCES

REPLY

WE ARE GRATEFUL FOR DR RANDLEMAN’S COMMENTS REGARDING OUR REPORT DEMONSTRATING THAT A CLAW-SHAPED PATTERN ON CORNEAL TOPOGRAPHY CAN BE FOUND NOT ONLY IN EYES WITH PELLUCID MARGINAL DEGENERATION (PMD), BUT ALSO, WITH SEEMINGLY GREATER PREVALENCE, IN EYES WITH KERATOCONUS.

In our report, we differentiated between cases that had definite keratoconus and those that had definite PMD. There was an in-between group for which we used rigorous criteria of subgrouping the cases into keratoconus suspects and PMD suspects. We agree with Dr Randleman’s concerns regarding the use of the term “suspect” in this context, because of the more common usage of the term “keratoconus suspect” to refer to cases in which the topographic patterns are not associated with clinical findings.

We also agree that this differentiation between keratoconus and PMD may be of limited usefulness in preoperative laser in situ keratomileusis evaluation, but this should not detract from its value in providing patients with a correct diagnosis (by relying on clinical examination in conjunction with topography). Our findings also are valuable to help surgeons in the decision-making process when penetrating keratoplasty is contemplated.

DIMITRI T. AZAR  
BRANDON W. LEE  
ULA V. JURKUNAS  
MONA HARISSI-DAGHER  
ANTONY M. POOTHULLIL  
FAISAL M. TOBAIGY  
Chicago, Illinois

Prostaglandin E₂ Inhibition and Aqueous Concentration of Ketorolac 0.4% and Nepafenac 0.1% in Patients Undergoing Phacoemulsification

EDITOR:

AFTER REVIEWING THE OFF-LABEL STUDY BY BUCCI AND ASSOCIATES COMPARING AQUEOUS HUMOR CONCENTRATIONS OF BOTH PGE₂ AND STUDY DRUG IN EYES PREOPERATIVELY Dosed WITH NEPAFENAC 0.1% OR KETOROLAC 0.4%, 1 I FEEL COMPELLED TO SHARE MY OBSERVATIONS.

First, I question why 50 of the 132 patients’ data were excluded from the PGE₂ analysis. Secondly, the authors report that eyes treated with ketorolac 0.4% had lower aqueous humor PGE₂ levels than those treated with nepafenac 0.1%. However, aqueous humor was sampled at the time of initial incision of cataract surgery, when PGE₂ levels have no relevance to surgically-induced inflammation. It takes hours to achieve elevated PGE₂ levels as a result of ocular insult. 2,3 Therefore, these results measuring the PGE₂ concentration at the onset of surgery provide no insight into the anti-inflammatory activity of either NSAID. Furthermore, PGE₂ levels can only show relative inhibition of study drugs if differences between pretreatment and posttreatment concentrations are compared. Because this study measured the PGE₂ concentration at only one time point, the claim that ketorolac has greater inhibitory activity than nepafenac cannot be substantiated.

With respect to the measurement of aqueous humor drug concentrations, it should be noted that the pulse administration of four drops of non-steroid anti-inflammatory drug (NSAID) prior to surgery is not standard of practice. Thus, there is no justification to presume the reported drug concentrations are clinically meaningful.

Even if one accepts the reasoning that the drug concentrations reported have clinical relevance, the conclusion that ketorolac 0.4% (Acular LS; Allergan, Inc, Irvine, California, USA) demonstrated superior aqueous humor penetration relative to nepafenac 0.1% (Nevanac; Alcon Laboratories, Fort Worth, Texas, USA) is false because it ignores nepafenac pharmacokinetics. As a prodrug, nepafenac is intraocularly converted to the potent NSAID, amfenac. Since the aqueous humor localization of both molecules is a direct result of nepafenac penetration, the concentrations of amfenac and nepafenac must be combined to accurately assess the aqueous penetration of Nevanac. Therefore, the authors’ statement that ketorolac was present at higher levels than either nepafenac or amfenac is misleading. The relevant measure of Nevanac penetration, the combined nepafenac and amfenac concentration, was 941.8 ng/ml, likely not statistically different from the ketorolac concentration of 1079.1 ng/ml. In fact, a multicenter study comparing the pharmacokinetics of one drop of Nevanac and Acular LS reported the
combined nepafenac + amfenac concentration was significantly greater than that of ketorolac over four hours following drug instillation.4

Bucci and associates negatively view the presence of nepafenac in the aqueous humor, suggesting that amfenac conversion occurring after surgery would not be useful in preventing surgically-induced inflammation. In contrast, I contend that this nepafenac reservoir is beneficial, contributing to prolonged anti-inflammatory activity, as shown by several clinical studies (Nardi M et al. IOVS 2007;48:ARVO E-Abstract B684).4,5

In conclusion, Bucci and associates suggest “the prodrug nature of nepafenac does not confer an advantage with regard to ocular penetration and PGE2 inhibition.” However, when one considers the subset of PGE2 data presented, the single time point of PGE2 assessment, the non-standard pulse NSAID dosing, as well as the decision to compare ketorolac concentration to that of each Nevanac analyte separately, the validity of their findings is questioned.

TOM WALTERS
Austin, Texas

REFERENCES
1. Bucci FA Jr, Waterbury LD, Amico LM. Prostaglandin E2 inhibition and aqueous concentration of ketorolac 0.4% (Acular LS) and nepafenac 0.1% (Nevanac) in patients undergoing phacoemulsification. Am J Ophthalmol 2007;144:146–147.

REPLY

WE APPRECIATE DR WALTER’S INTEREST IN OUR STUDY, “PGE2 Inhibition and Aqueous Concentration of Ketorolac 0.4% (Acular LS™) and Nepafenac 0.1% (Nevanac™) in Patients undergoing Phacoemulsification.”

Dr Walters states that PGE2 levels sampled at the outset of surgery are not relevant to inflammation induced by surgery. While the PGE2 levels at the start of surgery are likely not nearly as high as those induced following surgery, this sampling method represents a valid model for evaluating prostaglandins. Even at presumed lower prostaglandin levels at the start, ketorolac was still able to achieve a statistically significant treatment effect relative to nepafenac for reducing PGE2 levels.

I am somewhat surprised by Dr Walters’ statement that the dosing regimen used in this trial is not standard practice. This regimen is standard dosing protocol in my office and for many ophthalmologists. A study by Donnenfeld and associates demonstrated that pulse dosing of topical ketorolac one hour prior to surgery was effective in reducing postoperative inflammation following phacoemulsification.2

Dr Walters questions why 50 patients were excluded from the PGE2 analysis. In fact, PGE2 analyses were simply performed on the first 82 consecutive patients enrolled in the study while aqueous concentrations were evaluated for the entire 132-patient sample.

Dr Walters suggests that the aqueous concentrations of both amfenac and nepafenac should be added together to determine the actual aqueous concentration of nepafenac. This arithmetic seems questionable as there is no data to demonstrate that the totality of the nepafenac that reaches the aqueous is ultimately converted to amfenac. Ironically, the clinical trial Dr Walters cites as providing evidence for the need to combine the concentrations of both nepafenac and amfenac is based on a study measuring the effects of a single drop.1 Regardless of the intended use, a single drop is typically not representative of a dosing strategy with a topical non-steroid anti-inflammatory drug (NSAID). Unfortunately, any additional review of the data from the study in which Dr Walters participated is not possible at the present time as it has yet to be published.

Finally, Dr Walters contends that there are three clinical trials showing that a “reservoir” of unconverted nepafenac contributes to a prolonged anti-inflammatory effect. I reviewed two of the three citations that have been either presented or published2 (Nardi M et al. IOVS 2007;48: ARVO E-Abstract B684) and do not find this to be an accurate statement. Both trials evaluated cell and flare as primary efficacy variables and no data were presented to demonstrate a continuous conversion of amfenac from nepafenac. The third study cited by Dr Walters was pending publication so I have not reviewed it.3

In conclusion, I contend that our findings demonstrate that ketorolac 0.4% does inhibit PGE2 synthesis and penetrate into aqueous to a greater extent than nepafenac 0.1% in patients treated prior to cataract surgery.

FRANK A. BUCCI, JR
Wilkes-Barre, Pennsylvania

REFERENCES
1. Bucci FA Jr, Waterbury LD, Amico LM. Prostaglandin E2 inhibition and aqueous concentration of ketorolac 0.4% (Acular LS) and nepafenac 0.1% (Nevanac) in patients undergoing phacoemulsification. Am J Ophthalmol 2007;144:146–147.