An Alternative to Topical Dosing to Deliver Drugs to Target Tissues

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To the Editor,

I READ WITH CONSIDERABLE INTEREST a recent review entitled “Posterior Segment Drug Delivery Devices: Current and Novel Therapies in Development” by Bansal et al.¹ The article mentions the limitations of topical and oral dosing, and the risks inherent in direct injections into the posterior segment. It goes on to describe many possible devices for drug delivery to the posterior segment. Cataract surgery may be indicated when lens opacities interfere with the treatment of posterior segment diseases, or the cataract interferes with vision.

An obvious approach not discussed in the mentioned publication would be the addition of drugs to the irrigation solution during surgery. This has already been accomplished, and an approved drug (OMIDRIA[®]) that contains ketorolac and phenylephrine has been available for more than 1 year in the United States.² This combination is used

to maintain pupil size by preventing intraoperative miosis and to reduce postoperative pain.

Ketorolac concentrations in aqueous and vitreous have been determined using this product in a canine study as shown in Figure 1.³ Intraoperative dosing provides higher concentrations of ketorolac than topical dosing, persists for at least 10 h, and avoids the risks inherent in intraocular injections. It also provides adequate intraocular concentrations during a critical time immediately postoperatively.

These results have been compared with those from 2 clinical studies. A study by Katsev et al.³ indicated that although preoperative topically dosed ketorolac resulted in sufficient aqueous concentrations before surgery, most was lost during the surgical procedure (Fig. 1). This loss results from the filling of the anterior chamber with a viscoelastic material to stabilize the shape of the globe and by balanced salt solution used for irrigation as a standard part of cataract surgery. Despite this, aqueous humor drug concentrations immediately

FIG. 1. This figure combines 3 separate studies. They are a dog pharmacokinetic study (Florio et al.³), a clinical study by Katsev et al.,⁴ and a clinical study by Heier et al.⁵ Ketorolac concentrations (ng/g ± SEM) are graphed on a log scale. The drug pharmacokinetic study shows ketorolac concentration at 2 and 10 h in aqueous humor after intracameral dosing in the dog. These results are compared with those of Katsev et al.⁴ before and after surgery, and with vitreous levels in patients undergoing vitrectomies (Heier et al.⁵). Means were obtained from the Katsev results by assigning numeric values of 0.50 to those values less than the limits of detection (1 ng/mL). Note the striking differences before and after lens surgery in the Katsev study, and the low concentrations in vitreous after topical dosing (Heier et al.⁵). Ketorolac concentrations are less than that required for a 50% of COX-1 or COX-2 after surgery with topical dosing as well as in vitreous. IC₅₀ values are 5.1 and 30.7 ng/mL, respectively, for human recombinant COX-1 and COX-2, data not shown (Waterbury et al.⁶).

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before surgery are frequently promoted as advantageous in numerous publications including my own.

A second comparison revealed that the amount of ketorolac present in vitreous after topical dosing in patients undergoing vitrectomies was less than the reported human IC_{50} for COX-1 of 5.1 ng/mL, whereas intracameral dosing is sufficient to block COX-1 and COX-2 for at least 10 h postdosing. Topical dosing makes the drugs unavailable as anti-inflammatory agents when needed in critical sites such as the iris–ciliary body responsible for prostaglandin synthesis, and also for transport into the posterior chamber.

Although the implants and various devices described in this article may provide continued effective drug concentrations for certain chronic diseases of the posterior segment, it is uncertain whether such treatment is warranted when comparing possible risks versus benefits in surgical patients for whom healing is often uneventful. Nonetheless even with these patients, effective drug concentrations are needed to reduce the likelihood of complications such as cystoid macular edema and adequate drug levels are achieved with intracameral dosing during cataract surgery and for at least several hours afterward. Sometimes more direct approaches are overlooked by our increasing use of new devices. Perhaps topical dosing for patients before cataract surgery needs to be discontinued and substituted with drugs administered during the surgery.

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Received: June 9, 2016

Accepted: November 1, 2016

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