TWO CLINICAL TRIALS OF AN INTRAOCULAR STEROID DELIVERY SYSTEM FOR CATARACT SURGERY*

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ABSTRACT

Purpose: To determine the safety and efficacy of an intraocular dexamethasone drug delivery system (Surodex) in the treatment of inflammation following cataract surgery.

Methods: Surodex is a biodegradable polymer that releases dexamethasone for 7 to 10 days after placement in the anterior segment. Study 1 was a prospective, randomized, double-masked Phase II clinical trial of 90 cataract surgical patients that compared treatment with Surodex to treatment with a placebo drug delivery system and to no anti-inflammatory drug treatment at all. Study 2 was a separate prospective, randomized, double-masked study of 60 cataract surgical patients that compared treatment with Surodex to topical dexamethasone (eye drop) therapy.

Results: In the first study, Surodex was superior to placebo in suppressing postsurgical inflammation throughout the 60-day postoperative period, as judged by masked-evaluator, slit-lamp grading of cell and flare. The differences were statistically significant from postoperative day 3 through postoperative week 3. The majority of Surodex patients did not require topical steroid by 2 weeks after surgery (93%) or by 2 months after surgery (88%). In the second study, Kowa laser flare meter readings were lower in Surodex patients throughout the 90-day postoperative period. The results were statistically significant at 4, 8, and 15 days following surgery. There were no significant adverse complications of Surodex in either study.

Conclusion: Surodex was safe and effective in suppressing postcataract surgery inflammation and appears to be a promising alternative to topical steroids.

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INTRODUCTION

The use of perioperative anti-inflammatory medication for cataract surgery continues to be standard practice. The goal is to suppress and eliminate the variable amount of postoperative iridocyclitis and patient discomfort resulting from intraocular surgery. Options for drug administration at the time of surgery include topical drops, subconjunctival injection, collagen shield, and intracameral injection or infusion.[1] However, all of these methods fail to provide a therapeutic drug level of more than several hours' duration. For this reason, topical anti-inflammatory medication is routinely prescribed for several weeks postoperatively until the blood-aqueous barrier is reestablished.[2,3]

Poor corneal penetration may limit the drug level attainable via the topical route. Other disadvantages of topical therapy include problems with patient compliance, patient inconvenience, and patient instruction. Patient compliance problems may result in improper dosing and frequency, improper cul-de-sac instillation, improper preparation (eg, bottle contamination or failure to shake a suspension), and substitution of the wrong medication.[4,5] In some underdeveloped areas of the world, the problems of cost and availability may preclude the use of postoperative medication altogether.

Oculex Pharmaceuticals, Inc (Sunnyvale, Calif) has developed a unique sustained-release intraocular drug delivery system (DDS). The DDS is composed of a biodegradable lactic acid/glycolic acid copolymer combined with an active drug, which is inserted into the eye at the conclusion of surgery. The polymer is hydrolyzed into the natural by-products of lactic and glycolic acid. The active drug is gradually released at a controlled rate as the polymer dissolves. Depending on the formulation, the drug can be released over the course of a week or over several months.

The first DDS product developed by Oculex was Surodex (dexamethasone anterior segment drug delivery system), which contains 60 µg of dexamethasone. This is approximately the same amount of drug contained in one drop of topical 0.1% dexamethasone eye drops. Because of poor corneal penetration, only a small percentage of topically applied dexamethasone ever reaches the anterior chamber (AC).[6] While the aqueous dexamethasone level rapidly declines within hours of eye drop instillation, Surodex provides a continuous release of dexamethasone for 7 to 10 days. Surodex has been shown in rabbit studies to achieve a peak aqueous dexamethasone level of up to 2.10 µg/mL in the first 24 hours after implantation, with concentrations of 0.10 to 0.36 over the next 9 days (Oculex Pharmaceuticals, unpublished data). After this period, the dexamethasone level falls to low or nondetectable levels.

A Phase I study found no significant adverse effects related to Surodex in 6 patients following cataract surgery. The purpose of this paper is to present the results from the first 2 randomized, controlled clinical trials evaluating the safety and efficacy of this product.

METHODS

The protocol and informed consent forms for both clinical trials were approved by the Institutional Review Board or Ethics Committee at each investigational site. Study eligibility was similar for both trials. Adult patients scheduled to undergo cataract surgery who gave informed consent were eligible to participate. Patients with a history of uveitis or concurrent anterior segment disease were excluded from both studies. Study subjects were prohibited from using systemic steroidal or nonsteroidal anti-inflammatory drugs (NSAIDs) during the study period.

CLINICAL TRIAL I (US PHASE II)

Ninety eyes of 90 patients at 4 investigational sites were enrolled into the study upon the completion of uncomplicated phacoemulsification-IOL surgery. Patients who experienced any intraoperative complications, such as hemorrhage, vitreous loss, or posterior capsule rupture, were not eligible for enrollment. Patients were randomized in a 2:1 ratio into an active treatment group or a control group. All 60 patients in the active treatment group receive Surodex. By random determination, one half of the active treatment group received a single Surodex and one half received 2 Surodex. This allowed for a comparison of the efficacy of 2 different doses. Of the 30 control subjects, one half were randomized to receive a placebo DDS containing no dexamethasone, and the other half received no anti-inflammatory treatment or DDS.

At the conclusion of uncomplicated phacoemulsification-IOL surgery, eligible patients were randomized into 1 of the 4 study subgroups listed above. The Surodex or placebo DDS was placed behind the iris in the posterior chamber by the surgeon, so that it was concealed from the postoperative slit-lamp examiner. In this manner, the postoperative examiners, who were separate from the surgeons, were masked as to the treatment status. Because the placebo DDS and Surodex were indistinguishable by appearance, the masking was still maintained in the event that a single DDS migrated into the AC during the postoperative period. Patients were also masked as to the treatment they received at the time of surgery.

In addition to a preoperative baseline assessment, masked patient examinations were performed at postoperative days 1, 3, 7, 14, 21, 30, and 60. Patients were asked to grade their level of pain, discomfort, photo-

phobia, and lacrimation. The amount of conjunctival erythema, ciliary flush, corneal edema, and AC cell and flare were graded by slit-lamp examination. In addition to noting signs of inflammation, assessments were made of the best corrected visual acuity, intraocular pressure, and any abnormalities of the wound, cornea, iris, or fundus at each visit. Any adverse events were recorded and characterized.

Topical antibiotics were permitted during the perioperative period. However, no ocular or systemic anti-inflammatory medications were allowed for 2 weeks before surgery, during surgery, or immediately after surgery. By the third postoperative day, the masked postoperative examiner was allowed to initiate any postoperative anti-inflammatory therapy deemed necessary to treat ocular inflammation that was failing to improve. This was termed rescue medication.

Statistical Methods

Analysis of efficacy parameters was based on the original assigned treatment group. Safety parameters were analyzed on the basis of the treatment actually received. A two-way analysis of variance (ANOVA) model was used for the analysis of AC cell and flare by study visit.[7]

CLINICAL TRIAL II (SINGAPORE)

Sixty eyes of 60 patients at one investigational site were enrolled in the study following planned extracapsular cataract surgery by 1 of 2 surgeons. One half of the patients were randomized to receive a single Surodex at the conclusion of uncomplicated surgery. This was placed in the 6-o'clock position of the inferior AC angle so that it was not easily seen at the slit-lamp examination without gonioscopy.

The Surodex patients were placed on a regimen of normal saline placebo eye drops 4 times a day for 30 days postoperatively. The remaining patients were treated with dexamethasone 0.1% eye drops 4 times a day for 30 days postoperatively. These patients composed the topical dexamethasone group. To mask the treatment, identical bottles and labeling were used for the dexamethasone and placebo eye drops. Because the postoperative examiners were separate individuals from the surgeons, both the patients and the examiners were masked as to the treatment assignment.

All patients were treated with topical chloramphenicol 0.5% eye drops 4 times a day for 30 days. Oral acetazolamide, 500 mg, was routinely given at the conclusion of surgery followed by 250 mg, twice a day, for 48 hours. Oral anti-inflammatory medications were not allowed.

In addition to a preoperative baseline assessment, masked patient examinations were performed at postoperative days 1, 2, 4, 8, 15, 30, and

90, and at 1 year. Patients were asked to grade their level of pain, discomfort, photophobia, and lacrimation. The amount of conjunctival erythema, ciliary flush, and AC cell and flare were graded by slit-lamp examination.[8] In addition to signs of inflammation, assessments were made of the best corrected visual acuity and intraocular pressure. Adverse events were recorded and characterized.

The Kowa FM500 Laser Flare Meter (Kowa Co Ltd, Tokyo, Japan) was used to perform laser flare meter measurements at the baseline visit and at each postoperative visit except for the 1-year examination. Central endothelial cell specular microscopy was performed with the Konan NONCON ROBO noncontact specular microscope (Konan, Osaka, Japan) on the last 29 patients enrolled, of which 17 were from the Surodex group and 12 were from the topical dexamethasone group. Central endothelial specular microscopy was performed again on these patients at the day 90 visit. The 55 patients who returned for the 1-year visit had both central and peripheral endothelial specular microscopy performed.

Statistical Methods

Data were analyzed according to the originally assigned treatment. The primary efficacy variable was degree of flare, as measured by the laser flare meter and analyzed with the Wilcoxon signed-rank test.

RESULTS

There were no statistically significant differences in age, race, or sex between the different treatment groups in either of the 2 studies. The mean age of the study population was 73 years in study 1 and 67 years in study 2.

CLINICAL TRIAL I (US PHASE II) RESULTS

Ninety patients were enrolled in the 4 treatment arms of the study following surgery. Thirty-one patients received 2 Surodex, 29 patients received one Surodex, 14 patients received a placebo DDS, and 16 patients received no treatment. One patient who received one Surodex withdrew following surgery, leaving a total of 59 patients who completed the 2-month postoperative study period.

After day 1, there were no statistical differences in AC cell or AC flare scores between those patients receiving 1 and those receiving 2 Surodex, or between the 2 control subgroups (Table I). Therefore, for the purpose of statistically comparing active treatment versus control, the 2 Surodex subgroups were combined and the 2 control subgroups were combined.

As shown in Table II, Surodex was highly effective in the early and sus-

TABLE I: STUDY I. ANALYSIS OF OBSERVED ANTERIOR CHAMBER CELL AND FLARE BY TREATMENT GROUP

	ACTIVE GROUPS			CONTROL GROUPS		
	TWO SURODEX (N = 30)	ONE SURODEX (N = 30)	P VALUE* (TWO SURODEX VS ONE SURODEX)	PLACEBO DDS (N = 15)	NO TREATMENT (N = 15)	P VALUE* (PLACEBO DDS VS NO TREATMENT)
	MEAN (SEM) OF ANTERIOR CHAMBER CELL AND FLARE SCORE†					
Day 1	4.0 (0.3)	4.9 (0.3)	.008	4.1 (0.4)	4.3 (0.4)	.661
n	29	30		15	15	
Day 3	2.2 (0.3)	2.8 (0.3)	.228	3.4 (0.4)	4.3 (0.5)	.197
n	30	28		15	14	
Week 1	1.5 (0.3)	1.2 (0.3)	.530	2.7 (0.4)	3.6 (0.4)	.081
n	28	28		15	15	
Week 2	0.9 (0.3)	0.8 (0.3)	.770	2.2 (0.5)	1.8 (0.5)	.590
n	28	27		13	13	
Week 3	0.7 (0.2)	0.6 (0.2)	.826	1.4 (0.3)	1.6 (0.4)	.766
n	29	27		15	13	
Month 1	0.4 (0.1)	0.3 (0.1)	.774	0.4 (0.2)	0.7 (0.2)	.184
n	30	28		15	15	
Month 2	0.3 (0.1)	0.2 (0.1)	.838	0.5 (0.2)	0.6 (0.2)	.661
n	30	26		14	15	

DDS, drug delivery system.

* Pairwise *P* value = *P* value for pairwise test of treatment effect of categorical outcome for two groups based on Type III analysis from model described below.

† Mean and SEM (standard error of mean) were estimated from ANOVA model that includes treatment center, center and treatment by center interaction factors.

tained suppression of postoperative inflammation. Patients receiving either one or two Surodex had a lower amount of AC cell and flare compared with the combined control subgroups from postoperative day 3 through postoperative day 60. The differences in mean combined AC cell and flare scores were statistically significant from day 3 through week 3. The Surodex treatment groups showed less conjunctival erythema and ciliary flush compared with the controls, with the differences reaching statistical significance from day 1 ($P<.001$ for both parameters) through week 2.[7]

The Surodex-treated groups had less corneal edema than the control groups, starting at postoperative day 3. The differences were statistically significant at weeks 1 and 2 (both $P<.001$). Finally, Surodex-treated patients reported less discomfort ($P<.001$), pain ($P=.006$), photophobia

TABLE II: STUDY I. ANALYSIS OF OBSERVED ANTERIOR CHAMBER CELL AND FLARE

	TREATMENT GROUP ACTIVE ONE AND TWO SURODEX (N = 60)	CONTROL PLACEBO DDS AND NO TREATMENT (N = 30)	P VALUE°
	MEAN (SEM) OF ANTERIOR CHAMBER CELL AND FLARE SCORE†		
Day 1	4.5 (0.2)	4.2 (0.3)	.424
n	59	30	
Day 3	2.5 (0.2)	3.8 (0.3)	.002
n	58	29	
Week 1	1.4 (0.2)	3.2 (0.3)	<.001
n	56	30	
Week 2	0.9 (0.2)	2.1 (0.4)	.004
n	55	26	
Week 3	0.7 (0.2)	1.5 (0.2)	.004
n	56	28	
Month 1	0.3 (0.1)	0.6 (0.1)	.110
n	58	30	
Month 2	0.2 (0.1)	0.5 (0.1)	.081
n	56	29	

DDS, drug delivery system.

° P values for test of treatment effect between two treatment groups were based on Type III analysis from model described below.

† Mean and SEM (standard error of mean) were estimated from ANOVA model that includes treatment, center and treatment by center interaction factors.

($P<.001$), and lacrimation ($P=.045$) at day 3 than the control patients. These statistical differences continued through week 1.[7]

Rescue medication (topical corticosteroids or NSAIDs) could be initiated on postoperative day 3, at the masked examiner's discretion. Patients in the control groups required anti-inflammatory rescue medication sooner and more frequently compared with the Surodex treatment groups (Table III). The percentages of control patients needing topical rescue medication compared to Surodex patients were 47% (14/30) versus 3% (2/59) by day 3, 80% (24/30) versus 7% (4/59) by week 2, and 83% (25/30) versus 12% (7/59) by the end of the 2-month study. The differences reached statistical significance ($P<.001$) at every postoperative visit from day 3 on. Rescue medication was initiated for 3 Surodex-treated patients

TABLE III: STUDY 1. CUMULATIVE ANTI-INFLAMMATORY MEDICATION USAGE FOR STUDY EYE BY VISIT

	TREATMENT GROUP ACTIVE ONE AND TWO SURODEX (N = 59)	CONTROL PLACEBO DDS AND NO TREATMENT (N = 30)	P VALUE*
	NO. (%) OF PATIENTS WHO RECEIVED RESCUE MEDICATION FOR STUDY EYE		
Day 3	2 (3%)	14 (47%)	<.001
Week 1	3 (5%)	22 (73%)	<.001
Week 2	4 (7%)	24 (80%)	<.001
Week 3	5 (9%)	25 (83%)	<.001
Month 1	7 (12%)	25 (83%)	<.001
Month 2	7 (12%)	25 (83%)	<.001

DDS, drug delivery system.

*P value for test of treatment effect of categorical outcomes between active and control groups based on CMH test for general association stratified by center.

(5%) after week 2 (one at day 21, two at day 30).

Adverse events were typical of those seen following cataract surgery and included posterior capsule opacity and eye discomfort. Adverse events were seen in similar frequencies in both the Surodex and the control patients.

CLINICAL TRIAL II (SINGAPORE) RESULTS

Thirty-two patients were enrolled in the Surodex treatment group, and 28 patients were enrolled in the topical dexamethasone (eye drop) treatment group. All 60 patients completed the 90-day follow-up period, and 55 patients returned for the 1-year follow-up visit.

Mean AC cell, mean AC flare, and mean combined cell and flare scores, as judged by masked slit-lamp examination, were slightly lower in the Surodex treatment group throughout the 90-day study period. However, the differences were not statistically significant (Table IV). Similarly, there was generally no significant difference between treatment groups in the amount of conjunctival erythema and ciliary flush.[9]

The preoperative mean laser flare meter values were similar for the 2 groups (6.72 photon counts/msec in the eye drop group and 6.51 photon counts/msec in the Surodex group). As seen in Table V, the mean laser flare values were significantly lower in the Surodex treatment group compared with the dexamethasone eye drop treatment group during the first

TABLE IV: STUDY II. SLIT-LAMP CELL AND FLARE INFLAMMATORY SCORES (N=60)

	TREATMENT GROUP	MEAN CELL SCORE (SD)	SIGNIFICANCE	MEAN FLARE SCORE (SD)	SIGNIFICANCE	MEAN COMBINED CELL AND FLARE SCORE(SD)	SIGNIFICANCE
Preoperative	Dexamethasone drops	0.00		0.00		0.00	
	Surodex	0.00		0.00		0.00	
Day 4	Dexamethasone drops	3.21 (0.94)		1.61 (0.50)		4.82 (1.31)	
	Surodex	3.34 (1.04)	(NS)	1.50 (0.51)	(NS)	4.72 (1.44)	(NS)
Day 8	Dexamethasone drops	2.39 (0.96)		1.50 (0.51)		3.89 (1.34)	
	Surodex	2.22 (1.04)	(NS)	1.28 (0.63)	(NS)	3.45 (1.50)	(NS)
Day 15	Dexamethasone drops	1.75 (0.84)		1.39 (0.63)		3.18 (1.36)	
	Surodex	1.63 (1.04)	(NS)	1.06 (0.80)	(NS)	2.69 (1.67)	(NS)
Day 30	Dexamethasone drops	1.07 (0.94)		0.82 (0.67)		1.96 (1.48)	
	Surodex	0.88 (0.83)	(NS)	0.56 (0.62)	(NS)	1.44 (1.22)	(NS)
Day 90	Dexamethasone drops	0.36 (0.56)		0.04 (0.19)		0.39 (0.74)	
Surodex	0.25 (0.44)	(NS)	0.03 (0.18)	(NS)	0.22 (0.49)	(NS)	

NS, not significant at P >.05; SD, standard deviation.

° Wilcoxon rank sum test.

30 days postoperatively. The differences were highly statistically significant ($P<.01$) at days 4, 8, and 15 and significant ($P<.05$) at day 30. The mean flare value dropped below 20 photon counts/msec by day 8 in the Surodex treatment group, but not until day 30 in the dexamethasone eye drop treatment group.

Patients who required additional steroid anti-inflammatory drugs were considered therapeutic failures. Five patients (5/28, 18%) in the dexamethasone eye drop group and one patient (1/32, 3%) in the Surodex group required additional steroid therapy.[9]

There was no statistically significant difference between treatment

TABLE V: STUDY 2. LASER FLARE METER VALUES (PHOTON COUNTS/MSEC) (N=60)

	TREATMENT GROUP	MEAN (SD)	MEDIAN (Q1-Q3)	P VALUE°
Preoperative	Dexamethasone drops	6.72 (1.72)	6.6 (5.5 – 7.9)	NS
	Surodex	6.51 (3.31)	5.8 (5.0 – 6.9)	
Day 4	Dexamethasone drops	46.9 (37.8)	34.6 (20.4 – 55.1)	P<.01
	Surodex	24.6 (12.1)	24.0 (12.5 – 30.5)	
Day 8	Dexamethasone drops	31.9 (20.9)	23.2 (17.7 – 41.3)	P<.001
	Surodex	16.9 (8.0)	15.3 (10.3 – 22.1)	
Day 15	Dexamethasone drops	28.0 (22.8)	20.7 (13.6 – 35.2)	P<.01
	Surodex	15.4 (8.1)	11.7 (9.7 – 21.0)	
Day 30	Dexamethasone drops	18.0 (11.9)	16.2 (10.5 – 21.6)	P<.05
	Surodex	14.4 (9.9)	9.7 (7.9 – 18.6)	
Day 90	Dexamethasone drops	10.8 (7.7)	9.2 (7.3 – 11.5)	NS
	Surodex	8.7 (6.1)	7.4 (5.8 – 9.5)	

NS, not significant at P>.05; SD, standard deviation.

° Wilcoxon rank sum test.

groups in the mean percent change from baseline in central corneal endothelial cell counts at either 3 months or 1 year postoperatively (n=29). In the 55 patients examined with endothelial specular microscopy 1 year postoperatively, no significant difference was seen between treatment groups in either central or inferior corneal endothelial cell counts.[9]

Postoperative adverse events were similar in both treatment groups and included posterior capsule opacification (both treatment groups), glaucoma in a diabetic patient (dexamethasone eye drop group), and a persistent wound leak (Surodex patient). In 3 early cases, the Surodex was embedded into the angle and peripheral iris tissue to prevent migration. Iris synechiae developed postoperatively. No other Surodex-related

adverse events were reported.

DISCUSSION

Although steroids are routinely used to treat postoperative inflammation following cataract surgery, there are few studies in the literature documenting the efficacy of this practice. When these studies were initiated, rimexalone (Vexol) was the only steroid that had been proved efficacious over placebo by a prospective randomized, controlled study.[10,11] It was, therefore, the only steroid approved for the treatment of postoperative inflammation by the US Food and Drug Administration. For this reason, study 1 (US Phase II) compared Surodex to no drug treatment.

Anti-inflammatory medication may not be required for every patient following uncomplicated cataract surgery. Indeed, in study 1, 17% of control patients required no such medication postoperatively. However, Surodex was highly effective in reducing and eliminating postoperative inflammation and was clearly superior to no treatment. Rabbit studies suggest that dexamethasone is released intraocularly by Surodex over a period of about 7 to 10 days. The majority (93%) of Surodex-treated patients in study 1 did not require any other anti-inflammatory therapy during the first 2 weeks postoperatively. In study 2, 18% of patients already receiving dexamethasone eye drops as study treatment required additional steroid therapy, compared to only 3% of Surodex patients.

Rebound inflammation after depletion of the dexamethasone in Surodex did not appear to be a frequent occurrence. An additional 5% of Surodex-treated patients were started on rescue anti-inflammatory medication at the third or fourth postoperative week in study 1. Since an insignificant intraocular level of dexamethasone would have been expected by this time, these patients may have required more prolonged therapy for either persistent or rebound inflammation. However, after week 2, the mean AC cell and flare scores continued to be lower in the Surodex-treated groups, even though the majority (>80%) of the control group patients were taking rescue medication during this time.

Additionally, in study 2, while the topical steroid group was receiving treatment for 30 days, the dexamethasone level in the Surodex-treated group should have been nondetectable after week 2. The fact that the mean laser flare value was no higher in the Surodex-treated group at day 30 also suggests that rebound inflammation was not a significant problem with Surodex.

Rabbit studies suggest that by bypassing the cornea, the intraocular Surodex is able to achieve a higher aqueous level of dexamethasone than is possible with topical eye drops. In addition, continuous exposure to dex-

amethasone is maintained by Surodex for about 7 to 10 days. This is in contrast to the fluctuation in the aqueous level that occurs between applications after topical administration of dexamethasone eye drops.[12,13]

Both studies support the potential superiority of Surodex over topical steroid therapy. When compared to the control group, the Surodex-treated group in study 1 showed lower mean AC cell and flare scores throughout the study period. This improvement was statistically significant at week 3, even though the majority of the control patients (80%) were taking topical rescue medication at that point.

Study 2 provides a more direct comparison of Surodex to topical steroid therapy. Although Surodex demonstrated no statistically significant advantage in reducing slit-lamp AC cell and flare scores, it was at least as effective as topical steroid by this criterion.

Laser flare photometry provides a more objective measurement of the degree of blood-aqueous barrier breakdown. Surodex was clearly superior to topical dexamethasone eye drops in reducing aqueous flare as measured with the flare meter. The differences were dramatic during the first 2 postoperative weeks. Additional larger studies comparing Surodex to topical steroids will clarify whether one treatment alternative is more efficacious than the other.

Surodex appears to be well tolerated. There were no ocular or systemic adverse effects attributable to the use of the polymer delivery system in either of these 2 clinical trials. There was no evidence of endothelial cell loss between 3 and 12 months in the Surodex-treated patients in study 2.

Since none of the Surodex subjects developed an elevated intraocular pressure beyond the first postoperative day in either study, the outcome of implanting Surodex in steroid responders has not yet been determined. It is possible that the short duration of drug administration might diminish this potential problem.

Reducing or eliminating the responsibility and burden of administering postoperative anti-inflammatory drops would be a significant benefit to most patients. Eliminating concern over patient drug compliance would also save physician and staff time otherwise spent instructing and monitoring patients receiving topical therapy.

Whether administering antibiotic or anti-inflammatory medications, an ideal perioperative drug delivery system for cataract surgery would have the following attributes. It would demonstrate superior efficacy by providing an adequately high and prolonged drug level at the desired site. It would be safe and would confine the drug action to the desired intraocular location. It would be compatible with topical anesthesia and immediate vision. It would be short-acting enough to diminish the risks from side effects or allergy, but long-acting enough to obviate the necessity for

postoperative topical therapy. Further studies are warranted to test whether Surodex is able to provide some or all of these benefits.

CONCLUSION

These 2 prospective, randomized, double-masked studies have demonstrated both the efficacy and safety of Surodex (dexamethasone drug delivery system) in the treatment of inflammation following cataract surgery. This product demonstrated the potential to substitute for topical steroids in the majority of patients undergoing uncomplicated cataract surgery. It was superior to topical dexamethasone in reducing AC flare postoperatively.

This concept of a biodegradable intraocular drug delivery system can be extended to many other drugs and potential ocular applications as well. An obvious companion product for intraocular surgery would be an antibiotic for endophthalmitis prophylaxis. Such products may become particularly important in developing parts of the world, where topical medications may not currently be available following intraocular surgery.

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DISCUSSION

DR NARSING A. RAO. I would like to congratulate Dr Chang and Dr Wong for their interesting clinical study on intracameral steroid delivery for the treatment of intraocular inflammation following cataract surgery. The authors indicate that the use of perioperative anti-inflammatory agents for cataract surgery continues to be standard practice mainly to eliminate postoperative iridocyclitis.

Surgical trauma can induce iridocyclitis by several mechanisms, including, for example, the release of prostaglandins with recruitment of neutrophils and macrophages. This process subsequently produces oxygen free radicals, proteolytic enzymes, and both cyclo-oxygenase and lipoxygenase metabolites of arachidonic acid.[1] These inflammatory mediators are known to amplify the inflammatory process, leading to clinically detectable perilimbal injection, flare, and cells in the anterior chamber.

Based on therapeutic interventional studies, it appears that cyclo-oxygenase products play a significant role in the induction of intraocular inflammation. These studies show a significant reduction of ocular inflammation following topical administration of the cyclo-oxygenase inhibitors ketorolac and diclofenac, which are nonsteroidal anti-inflammatory agents (NSAIDs).[2-4] Unlike these agents, corticosteroids have broader anti-inflammatory effects on both the cyclo-oxygenase and the lipoxygenase pathways of arachidonic acid, as well as on neutrophils and macrophages. It is interesting to note that in these studies, the NSAIDs were found to be as effective as corticosteroids, such as prednisolone or dexamethasone, in reducing ocular inflammation.[5-7] Such observations further suggest the importance of the cyclo-oxygenase pathway in the induction of ocular inflammation.

In their present randomized, double-masked study, Drs Chang and Wong evaluate the safety and efficacy of Surodex, an intraocular biodegradable polymer that releases dexamethasone for a period of 7 to 10 days. They compared the efficacy of Surodex with a placebo and with topical dexamethasone administration in patients who underwent cataract extraction. Those patients whose cataract extraction was performed in the United States underwent phacoemulsification; those seen in Singapore were treated by extracapsular cataract extraction. In both studies, Surodex was found to be safe and effective in suppressing intraocular inflamma-

tion. It is interesting that the study from Singapore shows a significant reduction of flare in those patients treated with Surodex compared to those patients who received topical dexamethasone. Although Surodex is efficacious in the treatment of intraocular inflammation and in eliminating frequent administration of topical anti-inflammatory agents, it has the potential to enhance the infectious process in the rare patient who develops postoperative endophthalmitis. Moreover, the study design did not address the possible long-term effects of Surodex, particularly its effects on cataract wound healing, progression of posterior capsule opacity, and development of glaucoma.

In conclusion, in this well-designed and clinically important study, the authors clearly demonstrate a new approach to the treatment of post-cataract extraction intraocular inflammation and the safety and efficacy of intraocular drug delivery by biodegradable agents. Although the authors did not discuss a potential beneficial effect of preventing the development of cystoid macular edema (CME) in some patients treated with Surodex, their data suggest that Surodex administration may reduce or eliminate the development of CME, since a significant reduction in flare was noted in their patients.

I have two questions for the authors: (1) Are the 60 patients in the present study the same group of patients reported from the Singapore National Eye Center?[8] and (2) Do the authors plan to extend the study to evaluate CME in patients treated with Surodex compared to those treated with topical steroids and/or NSAIDs?

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DR JOSE S. PULIDO. We have had the opportunity to use a 1-month biodegradable steroid delivery system developed by the Oculex Pharmaceutical Company in patients that have had severe PVR and were referred to me for further surgery. In this Phase I trial, we have found that the eyes are very quiet after surgery. They do not have a significant amount of fibrin. We are very optimistic about the use of these 1-month biodegradable steroid delivery systems in these cases.

DR RICHARD L. LINDSTROM. Are we sure that a little bit of inflammation in a postoperative patient is a bad thing? We are now using more and more expensive drugs and systems to reduce cell and flare determined by a Kowa flare and cell meter. I have participated in 4 of these studies, one in PRK, one in LASIK, and 2 in cataract surgery. In every case we could measure a mild reduction in inflammation in the early postoperative period, but in every one of these studies, the end result after 6 months was the same. Even just using artificial tears in the postoperative period did not result in an increased incidence of clinically significant CME or other complications. It seems that mild inflammation is the natural process of healing. Are we treating ourselves, or are we treating the patient? I'm not sure that we want to totally eliminate all inflammation. The end point of all these studies should be visual acuity, the absence of CME, and the absence of other complications, not just the reduction of flare and cells in the early postoperative period.

DR GEORGE A. STERN. In the early days of cataract surgery, people could not show that the use of steroids made any difference in the postoperative course of the patient. This may have changed slightly when we had poor intraocular implants, but now with good surgery and good implants, we are disappointed if we see any significant flare and cell shortly after the surgery. I'm not sure that the use of steroids makes any difference. Maybe you can show less flare with this system, but do the patients see any better, are there fewer complications, is the recovery faster, or are the patients more comfortable? Are there any complications associated with this delivery system? I'm not sure if this can be determined by a study of 80 to 90 patients. Has safety truly been established by this time?

DR WILLIAM M. BOURNE. I congratulate the authors for a very nice study.

I think this technique is promising. Does placing this 1-mm-diameter foreign body in the posterior chamber show any visible distortion of the iris, such as a bulge, or does it rub pigment from the iris and produce a Krukenberg spindle? Is the angle more pigmented?

DR ALLAN J. FLACH. I would like to know more about what other drugs were used, such as NSAIDs before surgery and viscosity agents during surgery. Would viscosity agents affect the ability of this system to release its drug? There is evidence that NSAIDs may act synergistically with dexamethasone to reduce inflammation. It might be interesting to compare this pellet with NSAIDs given topically, because some studies have shown that the nonsteroidal drugs are more effective in stabilizing the blood-aqueous barrier than steroidal drugs. I certainly agree with Dr Lindstorm and Dr Stern that we should be using medications for better vision. There is evidence that excessive inflammation is linked with postoperative angiographic CME. However, we do not know which of these patients will develop clinically significant CME. We do not want to treat patients for months and months to prevent angiographic CME just because a few will develop clinically significant CME. On the other hand, to deny the use of some postoperative anti-inflammatory agents does not make good sense either.

DR JOHN T. FLYNN. My question is a generic one. With all due respect to the retinal surgeons, we do not have a good technique for treating stage 4 and stage 5 retinopathy of prematurity. Will the use of this biodegradable system be of any value in possibly treating retinopathy of prematurity and preventing the devastating proliferation of tissue in this disease?

DR JAMES C. BOBROW. I, too, would like to congratulate Dr Chang and Dr Wong. Having operated on cataract patients in 4 continents, I can say that one of the most intriguing aspects of this technology is that we will be able to provide anti-inflammatory treatment to people who do not understand or cannot comply with a therapeutic regimen as easily as we would like. I do have a question about the possibility of using dexamethasone intraocularly. I am impressed that patients in both of the studies did not have a rise in intraocular pressure. I want to ask if patients who were known steroid responders were studied as a separate group. If so, did they develop glaucoma?

DR W. RICHARD GREEN. I have heard about this delivery system for a number of years; I am glad finally to see some clinical results. I had hoped that the authors would have concentrated on the delivery of other drugs,

such as antiviral and antibacterial agents, drugs for which there is more need for sustained release. How far are you from developing an antiviral agent for cytomegalovirus retinitis?

DR VERNON G. WONG. It was our hope to introduce a lively discussion, since the new platform for drug delivery discussed in our presentation is a controversial one.

Dr Rao, 60 of the patients reported in this study were previously reported by the Singapore National Eye Center, and the study has since been published in the February 1999 issue of Ophthalmology. We hope that intraocular Surodex will help prevent the development of CME in patients after surgery, but the series so far is too small to draw any definitive conclusions. However, there were no reported cases of CME in the 2 studies cited in today's presentation.

Dr Lindstrom, I don't think the question is whether we should treat a postoperative eye with little or mild inflammation. That is the prerogative of the physician. What is important is that Surodex has been shown to be very effective in reducing postoperative inflammation compared to standard treatment with drops, particularly in the diabetic eye. What is clear from these 2 studies is that the small amount of dexamethasone (60 µg) in Surodex is therapeutically effective for the entire postoperative course, and for the first time compliance is no longer an issue.

Dr Stern, patients with Surodex are reported to be much more comfortable postoperatively than those receiving eye drops. ln our Phase I (US) study, 3 of the patients felt comfortable enough to play golf during the first postoperative week. The outcome of visual acuity in Surodex-treated patients is no different from those receiving standard eye drops.

Dr Bourne, Surodex is very tiny, measuring approximately 0.38 x 1.0 mm. It has not been shown to have any adverse reaction when placed in the anterior chamber or in the posterior chamber. No Krukenberg spindles or increased angle pigmentation have been observed in any of the treated patients.

Dr Flach, no drug interactions have been reported thus far in the patients treated. Viscoelastics were used in all patients in these studies, but distinct differences in the clinical response to Surodex between the various types of viscoelastics have not been observed. In vitro studies with commercial viscoelastics did not appear to affect the dexamethasone release profile of Surodex. No studies of interactions between NSAIDS and Surodex have been performed.

Dr Flynn, I do not know whether the use of biodegradable implants will be a suitable way to treat retinopathy of prematurity in the future, but I think its use should be seriously considered. We have learned much

about the biodegradable implants in the eye and have found them to be safe clinically and experimentally. Therefore, their use in young patients and those with retinopathy of prematurity should be considered.

Dr Bobrow, we have not encountered glaucoma after surgery attributable to Surodex. A study with Surodex in known steroid responders has not been done.

Dr Green, we are currently working on various delivery systems for the posterior segment, including antibiotic, antiviral, and antimitotic agents.