

Vital Dyes for Staining Intraocular Membranes and Tissues During Vitrectomy

An overview of vital dyes and their characteristics.

BY MAURICIO MAIA MD, PhD; MICHEL EID FARAH, MD, PhD; EDUARDO B. RODRIGUES, MD;
ANDRÉ MAIA, MD; OCTAVIANO MAGALHÃES JR., MD; AND ACÁCIO LIMA, PhD

Dyes may be designated vital when they are used to stain living tissues or cells. In ophthalmology, vital dyes have become effective and useful surgical tools for identifying ocular tissues. Chromovitrectomy is a novel surgical technique for visualizing intraocular tissues during vitreoretinal surgery. This technique was introduced with the goal of avoiding ocular complications related to internal limiting membrane (ILM) peeling, inadequate removal of vitreous, and incomplete removal of the epiretinal membrane (ERM). Chromovitrectomy is credited with improving ILM peeling.¹⁻¹⁰ Since 2000, this technique has become popular among vitreoretinal specialists.⁹

Vital dyes contain a variety of chemical structures, including chromophores, the moiety responsible for a molecule's color.¹⁻¹⁰ Although chromophores are highly important in organic chemistry, their identification in vital dyes relevant to chromovitrectomy has not been well studied. This field of research is important because it may be possible to separate the chromophore from other parts of the molecule, resulting in safer vital dyes for the retina.¹⁻¹⁰

VITAL DYES

Triamcinolone acetonide. The state-of-the-art staining agent for identifying the vitreous is the white steroid triamcinolone acetonide.² Its crystals bind avidly to the vitreous gel, enabling visualization of a clear contrast between empty portions of the vitreous cavity and areas in which vitreous fibers are still present.^{11,12}

Triamcinolone acetonide is injected into the vitreous

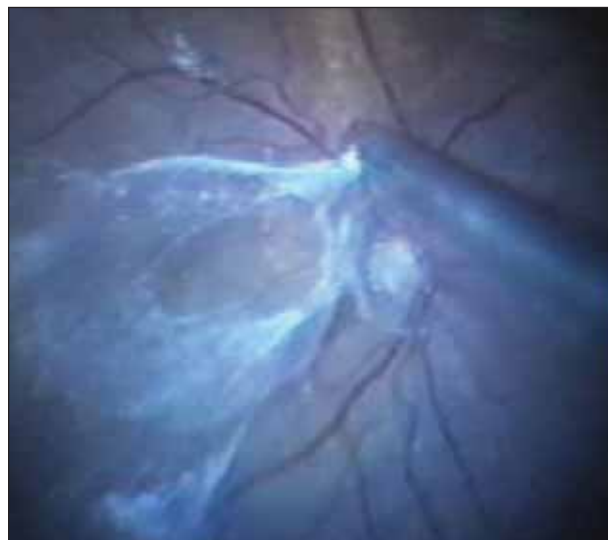


Figure 1. An intraoperative view of posterior hyaloid detachment surgery assisted by triamcinolone. The posterior hyaloid is detached from the optic nerve in an eye with diabetic retinopathy.

cavity toward the area to be visualized (0.1 to 0.3 mL, 40 mg/mL [4%] concentration). Injecting this steroid during vitrectomy for the management of retinal detachment may prevent fibrin reaction and proliferative vitreoretinopathy postoperatively.^{13,14,15,16} The steroid improves identification of tissue through the deposition of crystals, which helps the surgeon achieve complete detachment and removal of the posterior hyaloid and improves the results of primary vitrectomy for management of retinal

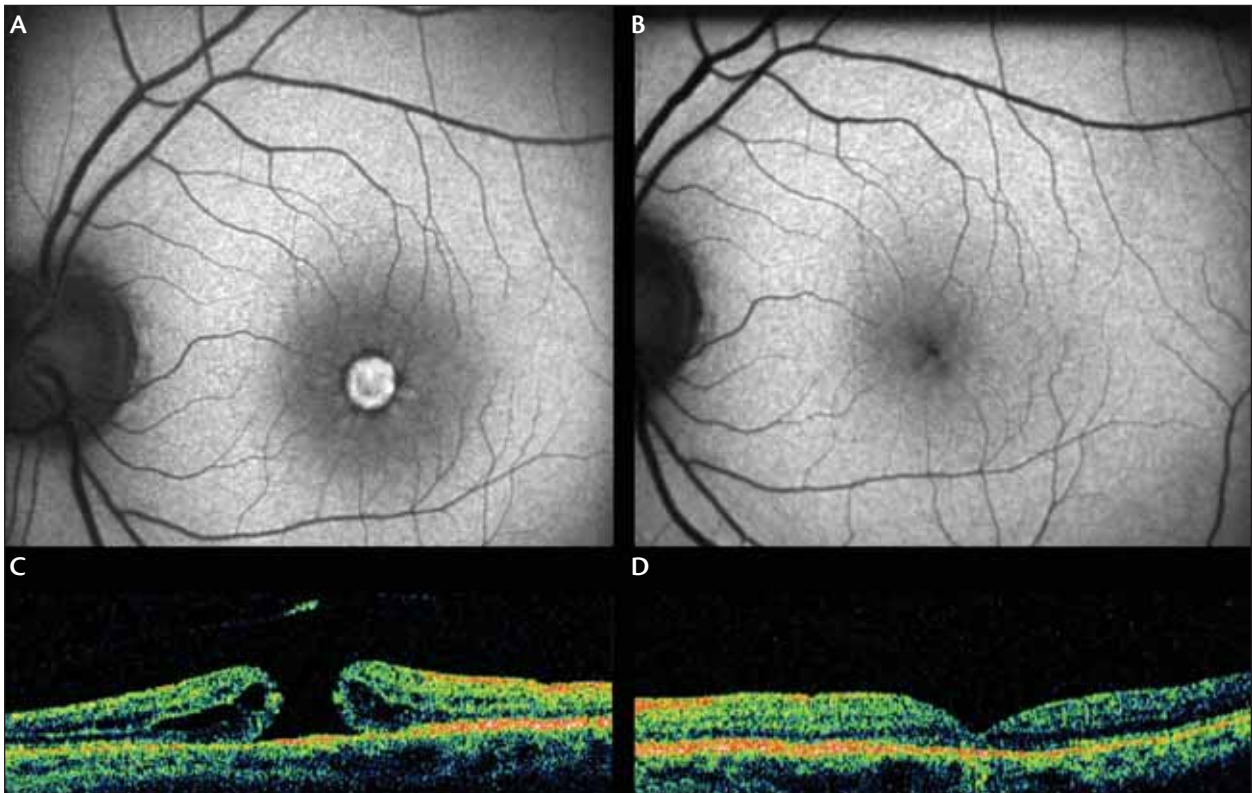


Figure 2. Autofluorescence and optical coherence tomography (OCT) images before macular hole surgery (A,C). Autofluorescence and OCT images after macular hole surgery and ILM peeling guided by 0.05% ICG staining (B,D). Note the absence of hyperautofluorescence image after surgery (B) and also the sealed hole by OCT (D). BCVA improved from 20/400 preoperative to 20/30 postoperative.

detachment and diabetic retinopathy in young patients (Figure 1).^{17,18}

Indocyanine green. Indocyanine green (ICG) and infra-cyanine green may be considered the gold standard dyes for staining and visualizing the ILM in surgical therapy for macular hole and diabetic macular edema. These dyes possess a great affinity for the matrix components of the ILM, such as collagen type 4 and laminin.^{2,19}

ICG-guided chromovitrectomy first gained worldwide popularity, and a number of studies showed ICG-guided peeling to be easier and less traumatic than surgery without ICG, demonstrating good clinical results in macular hole surgery. However, subsequent studies have revealed that ICG may be toxic to the retina. Clinical data showed that ICG can remain intravitreally or deposit persistently on the optic disc after surgery for macular hole. Studies also suggest that ICG can diffuse into the subretinal space through a macular hole, causing damage to the retinal pigment epithelium (RPE; Figure 2).^{20,21}

It has been postulated that the use of ICG at low concentrations in ILM peeling could be a safer alternative because lower rates of RPE abnormalities have been observed with

ICG at a concentration of 0.5 mg/mL (0.05%) or less, and an osmolarity of approximately 290 mOsm.²²

There are many hypotheses about why and how ICG may induce retinal damage. Intravitreal ICG injections may change the osmolarity in the vitreous cavity, thereby damaging either the neurosensory retina or the RPE cells directly.²³⁻²⁶ Investigations in various animal models have shown that ICG may be hazardous to the RPE or neuroretinal cells. Moderate to high doses (2.5 [0.025%] to 25 mg/mL [2.5%]) of intravitreal ICG were toxic to retinochoroidal cells, and impairment of retinal function was described even at low doses of ICG (0.025 mg/mL [0.0025%]; Figure 3).²⁶⁻²⁸

An ICG molecule has approximately 5% iodine in its final solution and no sodium or calcium.^{2,23,29} Nevertheless, it is has been suggested that removing sodium from the saline solution used for diluting the dye may decrease the risk of RPE damage.³⁰ It has been speculated that ICG injection into the vitreous cavity may absorb light; this interaction may lead to a photodynamic effect that induces retinal damage. It was demonstrated that subretinal ICG injection plus light exposure in rabbits can result in functional retinal damage and RPE changes.^{2,21,28,29}

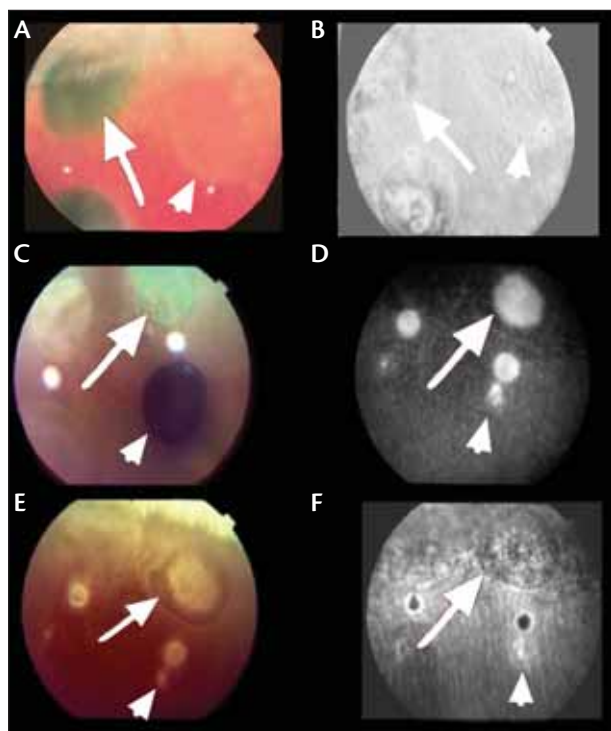


Figure 3. Fundus photographs after subretinal indocyanine green and trypan blue injection in rabbits. Fundus photograph 1 hour after subretinal injection of 0.5% ICG using a 41-gauge cannula (A; arrow and arrowhead). Fluorescein angiogram (B) 1 week after subretinal ICG injection (arrow) and subretinal saline injection (arrowhead) showing atrophic changes in positions related to previous subretinal injection of ICG (arrow). Fundus photograph 1 hour after subretinal ICG and TB injection (C). Fluorescein angiogram shows more substantial damage to RPE in positions related to previous subretinal ICG (D; arrow) compared with subretinal trypan blue (D; arrowhead). Fundus photograph 1 week after subretinal ICG (arrow) and trypan blue (arrowhead) injection (E). Fluorescein angiogram shows more substantial damage to RPE in positions related to previous subretinal ICG (F; arrow) compared with subretinal trypan blue (F; arrowhead). Source: Penha FM, Maia M, Eid Farah M et al. Effects of subretinal injections of indocyanine green, trypan blue, and glucose in rabbit eyes. *Ophthalmology*. 2007;114:899-908.

Once diluted in any solvent and exposed to light, ICG may undergo various chemical reactions by self-sensitized oxidation because it is chemically unstable; this phenomenon is called decomposition.³⁰ It was demonstrated that, independent of light exposure, singlet oxygen (photodynamic type 2 reaction) is generated by ICG, leading to dioxetanes by cycloaddition of singlet oxygen.³⁰⁻³² Furthermore, dioxetanes thermally decompose into several carbonyl compounds. Decomposition of ICG was

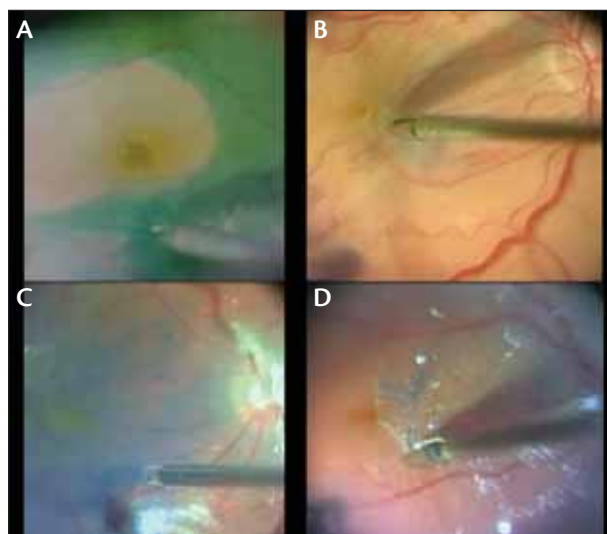


Figure 4. ILM peeling guided by ICG staining in macular hole surgery (A). ILM peeling guided by brilliant blue staining in a macular hole surgery (B). Technique of double staining using brilliant blue and triamcinolone acetonide injected over the retinal surface using a soft tip cannula while balanced salt solution infusion remained closed (C). ILM peeling guided by double staining technique after ERM removal. Staining was performed with 0.2 mL of 40 mg/mL triamcinolone along with 0.2 mL of 0.25% brilliant blue (D).

blocked by sodium azide, a quencher of singlet oxygen. This supports the rationale for future use of quenchers in chromovitrectomy.³⁰

Infracyanine green. Iodine and its derivatives may be toxic to the RPE.²³ Therefore, infracyanine green (IFCG), a dye free of iodine in its formulation either as free ion or as part of the dye moiety, is believed to have less potential for RPE toxicity than ICG.² With this presumably safer profile, IFCG may represent an alternative to ICG during ILM peeling in chromovitrectomy due to the lack of sodium iodine in its formulation and physiologic osmolality.^{2,23}

Brilliant blue. In humans, brilliant blue causes adequate ILM staining in an isoosmolar solution of 0.25 mg/mL (0.025%) to 0.50 mg/mL (0.05%) with good clinical results and no signs of toxicity on multifocal electroretinogram.² This stain has become a good alternative to ICG and IFCG in chromovitrectomy because of its remarkable affinity for the ILM. Toxicity data regarding its application are limited, so further investigations to confirm these observations are warranted. We have recently demonstrated that subretinal migration of brilliant blue may cause atrophic changes to the RPE.³⁴ Therefore, we strongly suggest avoidance of brilliant blue exposure to the RPE during chromovitrectomy.

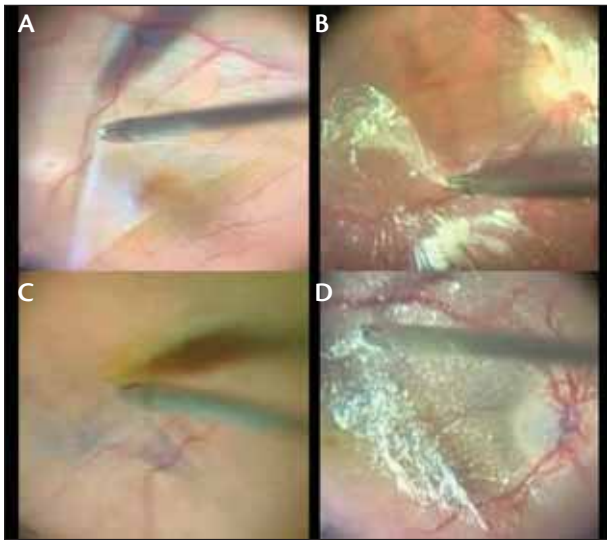


Figure 5. ERM peeling without dyes (A). ERM peeling using 0.2 mL of 40 mg/mL triamcinolone acetonide (B). ERM peeling using trypan blue (C). ERM peeling using the double staining technique with triamcinolone acetonide and trypan blue. Staining was performed with 0.2 mL of 40 mg/mL triamcinolone acetonide with 0.2 mL of 0.05% trypan blue (D).

However, we consider this dye the best one for ILM peeling in macular hole surgery. It is also used worldwide despite the fact that there are no clinical trials to support its use (unpublished data). This dye may be used without fluid-air exchange; additionally, no dilution in glucose is necessary.

Trypan blue. This dye may not enable ILM visualization as well as ICG, but this blue dye remains an alternative.² In order to enhance the staining properties of trypan blue, the dye may be injected into the posterior pole after fluid air exchange, or it may be mixed with glucose 5% to 10% to create a “heavy” trypan blue, which is denser than balanced salt solution.^{2,35} However, higher glucose concentrations should be avoided because glucose 50% has a highly toxic osmolarity of 2020 mOsm/L.² It is recommended that trypan blue be used mainly for ERM staining.^{2,35} Trypan blue has an affinity for epiretinal glial tissues such as the ERM. Therefore, we consider trypan blue the best dye for staining the ERM. It is suggested to mix 0.3 mL of trypan blue with 0.1 mL of glucose 10%, resulting in a 1 mg/mL (0.1%) solution with an osmolarity of 300 mOsm.^{2,33,35}

DOUBLE STAINING TECHNIQUE

The double-staining technique (Figures 4 and 5) is an elegant procedure that may facilitate the identification of the posterior hyaloid and ERM as well as the posterior

hyaloid and ILM. In this technique, a dye with a high affinity to the vitreous is injected to enable vitreous removal, followed by a second injection of a dye such as IFCCG, ICG, trypan blue, or brilliant blue, to stain and peel preretinal membranes.² As an alternative technique, two dyes may be injected at once before both peeling procedures. ■

Mauricio Maia, MD, PhD, is Assistant Professor of Ophthalmology, Vitreoretinal Surgery Unit at the Department of Ophthalmology, Vision Institute, Federal University of São Paulo, Brazil. He states that he receives funding from the Fundação de Amparo a Pesquisa do Estado de São Paulo (FAPESP) and the Pan-American Association of Ophthalmology (PAAO)/Pan-American Ophthalmological Foundation (PAOF). Dr. Mauricio Maia may be reached at retina@femane.com.br.



Eduardo B. Rodrigues, MD, is a Professor of Ophthalmology at the Department of Ophthalmology, Vision Institute, Federal University of São Paulo, Brazil, Department of Ophthalmology, Federal University of São Paulo in São Paulo, Brazil. He states that he receives funding from FAPESP and the PAAO/PAOF. Dr. Rodrigues may be reached at edubrodrigues@yahoo.com.br.



Michel Eid Farah, MD, PhD is Associate Professor of Ophthalmology, Vitreoretinal Surgery Unit at the Department of Ophthalmology, Vision Institute, Federal University of São Paulo, Brazil. He states that he receives funding from FAPESP and the PAAO/PAOF. Dr Farah may be reached at mefarah@uol.com.br.



André Maia, MD, is Professor of Ophthalmology, Vitreoretinal Surgery Unit at the Department of Ophthalmology, Vision Institute, Federal University of São Paulo, Brazil. He states that he receives funding from FAPESP and the PAAO/PAOF. Dr Andre Maia may be reached at maia@retina.com.br.



Acácio Lima, PhD, is Chief of Ocular Pharmacology Unit at the Department of Ophthalmology, Vision Institute, Federal University of São Paulo, Brazil. He states that he receives funding from FASEP and the PAAO/PAOF. Dr Lima may be reached at acaciolima@gmail.com.



Octaviano Magalhães Jr, MD, is Professor of Ophthalmology, Vitreoretinal Surgery Unit at the Department of Ophthalmology, Vision Institute, Federal University of São Paulo, Brazil. He states that he receives funding from FAPESP and the PAAO/PAOF. Dr Magalhães may be reached at octavianomj@terra.com.br.



1. Jacobs DS, Cox TA, Wagoner MD, et al. Capsule staining as an adjunct to cataract surgery: a report from the American Academy of Ophthalmology. *Ophthalmology*. 2006;113(4):707-713.
2. Rodrigues EB, Maia M, Meyer CH, Penha FM, Dib E, Farah ME. Vital dyes for chromovitrectomy. *Curr Opin Ophthalmol*. 2007;18(3):179-187.
3. Eckardt C, Eckardt U, Groos S, et al. Removal of the internal limiting membrane in macular holes. Clinical and morphologic findings. *Ophthalmologica*. 1997;94(8):545-51.
4. Rodrigues EB, Meyer CH, Farah ME, et al. Intravitreal staining of the internal limiting membrane using indocyanine green in the treatment of macular holes. *Ophthalmologica*. 2005;219(5):251-262.
5. Mester V, Kuhn F. Internal limiting membrane removal in the management of full-thickness macular holes. *Am J Ophthalmol*. 2000;129(6):769-777.
6. Kwok AK, Li WW, Pang CP, et al. Indocyanine green staining and removal of internal limiting membrane in macular hole surgery: histology and outcome. *Am J Ophthalmol*. 2001;132(2):178-183.
7. Engelbrecht NE, Freeman J, Sternberg P Jr, et al. Retinal pigment epithelial changes after macular hole surgery with indocyanine green-assisted internal limiting membrane peeling. *Am J Ophthalmol*. 2002;133(1):89-94.
8. Haritoglou C, Ganderfer A, Gass CA, Schaumberger M, Ulbig MW, Kampik A. Indocyanine green-assisted peeling of the internal limiting membrane in macular hole surgery affects visual outcome: a clinicopathologic correlation. *Am J Ophthalmol*. 2002;134(6):836-841.
9. Burk SE, Da Mata AP, Snyder ME, et al. Indocyanine green-assisted peeling of the retinal internal limiting membrane. *Ophthalmology*. 2000;107(11):2010-2014.
10. Feron EJ, Veckeneer M, Parys-Van Ginderdeuren R, Van Lommel A, Melles GR, Stalmans P. Trypan blue staining of epiretinal membranes in proliferative vitreoretinopathy. *Arch Ophthalmol*. 2002;120:141-144.
11. Koto T, Inoue M, Shinoda K, et al. Residual crystals of triamcinolone acetonide in macular hole may prevent complete closure. *Acta Ophthalmol Scand*. 2007;85:913-914.
12. Maia M, Penha FM, Farah ME, et al. Subretinal injection of preservative-free triamcinolone acetonide and supernatant vehicle in rabbits: an electron microscopy study. *Graefes Arch Clin Exp Ophthalmol*. 2008;246:379-388.
13. Peyman GA, Cheema R, Conway MD, et al. Triamcinolone acetonide as an aid to visualization of the vitreous and the posterior hyaloid during pars plana vitrectomy. *Retina*. 2000;20:554-555.
14. Hiebl W, Günther B, Meinert H. Substances for staining biological tissues: use of dyes in ophthalmology. *Klin Monatsbl Augenheilkd*. 2005;222:309-311.
15. Haritoglou C, Yu A, Freyer W, et al. An evaluation of novel vital dyes for intraocular surgery. *Invest Ophthalmol Vis Sci*. 2005;46:3315-3322.
16. Cheema RA, Peyman GA, Fang T, Jones A, Lukaris AD, Lim K. Triamcinolone acetonide as an adjuvant in the surgical treatment of retinal detachment with proliferative vitreoretinopathy. *Ophthalmic Surg Lasers Imaging*. 2007;38:365-370.
17. Maia M, Farah ME, Belfort RN, et al. Effects of intravitreal triamcinolone acetonide injection with and without preservative. *Br J Ophthalmol*. 2007;91:1122-1124.
18. Abrams GW, Topping T, Machemer R. An improved method for practice vitrectomy. *Arch Ophthalmol*. 1978;96:521-525.
19. Wollensak G, Spoerl E, Wirtzbauer C, et al. Influence of indocyanine green staining on the biomechanical strength of porcine internal limiting membrane. *Ophthalmologica*. 2004;218:278-282.
20. Tadayoni R, Paques M, Girmens JF, et al. Persistence of fundus fluorescence after use of indocyanine green for macular surgery. *Ophthalmology*. 2003;110:604-608.
21. Maia M, Haller JA, Pieramici DJ, et al. RPE abnormalities after ILM peeling guided by ICG staining. *Retina*. 2004; 24:157-160.
22. Rodrigues EB, Meyer CH. Meta-analysis of chromovitrectomy with indocyanine green in macular hole surgery. *Ophthalmologica*. 2008;222:123-129.
23. Penha FM, Maia M, Farah ME, et al. Morphologic and clinical effects of subretinal injection of indocyanine green and intracranial anesthetic in rabbits. *J Ocul Pharmacol Ther*. 2008;24:52-61.
24. Stalmans P, Van Aken EH, Veckeneer M, Feron EJ, Stalmans I. Toxic effect of indocyanine green on retinal pigment epithelium related to osmotic effects of the solvent. *Am J Ophthalmol*. 2002;134:282-285.
25. Marmor MF. Retinal detachment from hyperosmotic intravitreal injection. *Invest Ophthalmol Vis Sci*. 1979;18:1237-1244.
26. Penha FM, Maia M, Eid Farah M, et al. Effects of subretinal injections of indocyanine green, trypan blue, and glucose in rabbit eyes. *Ophthalmology*. 2007;114:899-908.
27. Enaida H, Sakamoto T, Hisatomi T, et al. Morphological and functional damage of the retina caused by intravitreal indocyanine green in rat eyes. *Graefes Arch Clin Exp Ophthalmol*. 2002;240:209-213.
28. Maia M, Kellner L, de Juan E Jr, et al. Effects of indocyanine green injection on the retinal surface and into the subretinal space in rabbits. *Retina*. 2004;24:80-91.
29. Costa E, Rodrigues EB, Farah ME, et al. Vital dyes and light sources for chromovitrectomy: comparative assessment of osmolarity, pH, and spectrophotometry. *Invest Ophthalmol Vis Sci*. 2009;50(1):385-391.
30. Engel E, Schraml R, Maisch T, et al. Light-induced decomposition of indocyanine green. *Invest Ophthalmol Vis Sci*. 2008;49:1777-1783.
31. Ho JD, Chen HC, Chen SN, et al. Reduction of indocyanine green-associated photosensitizing toxicity in retinal pigment epithelium by sodium elimination. *Arch Ophthalmol*. 2004;122:871-878.
32. Kadosono K, Takeuchi S, Yabuki K, et al. Absorption of short wavelengths of endoillumination in indocyanine green solution: implications for internal limiting membrane removal. *Graefes Arch Clin Exp Ophthalmol*. 2003;241:284-286.
33. Uno F, Malerbi F, Maia M, Farah ME, Maia A, Magalhães O Jr. Subretinal trypan blue migration during epiretinal membrane peeling. *Retina*. 2006;26(2):237-239.
34. Maia M, Farah ME, Rodrigues EB, et al. Subretinal brilliant blue G migration during internal limiting membrane peeling. *Br J Ophthalmol*. 2009;93(12):1687.
35. Maia M, Penha F, Rodrigues EB, et al. Effects of subretinal injection of patent blue and trypan blue in rabbits. *Curr Eye Res*. 2007;32(4):309-317.

INDICATIONS AND USAGE

NEVANAC® ophthalmic suspension is indicated for the treatment of pain and inflammation associated with cataract surgery.

CONTRAINDICATIONS

NEVANAC® ophthalmic suspension is contraindicated in patients with previously demonstrated hypersensitivity to any of the ingredients in the formulation or to other NSAIDs.

WARNINGS

There is the potential for cross-sensitivity to acetylsalicylic acid, phenylacetic acid derivatives, and other nonsteroidal anti-inflammatory agents. Therefore, caution should be used when treating individuals who have previously exhibited sensitivities to these drugs.

With some nonsteroidal anti-inflammatory drugs including NEVANAC®, there exists the potential for increased bleeding time due to interference with thrombocyte aggregation. There have been reports that ocularly applied nonsteroidal anti-inflammatory drugs may cause increased bleeding of ocular tissues (including hyphemas) in conjunction with ocular surgery.

PRECAUTIONS

General: Topical nonsteroidal anti-inflammatory drugs (NSAIDs) including NEVANAC®, may slow or delay healing. Topical corticosteroids are also known to slow or delay healing. Concomitant use of topical NSAIDs and topical steroids may increase the potential for healing problems.

Use of topical NSAIDs may result in keratitis. In some susceptible patients, continued use of topical NSAIDs may result in epithelial breakdown, corneal thinning, corneal erosion, corneal ulceration or corneal perforation. These events may be sight threatening. Patients with evidence of corneal epithelial breakdown should immediately discontinue use of topical NSAIDs including NEVANAC® and should be closely monitored for corneal health.

Postmarketing experience with topical NSAIDs suggests that patients with complicated ocular surgeries, corneal denervation, corneal epithelial defects, diabetes mellitus, ocular surface diseases (e.g., dry eye syndrome), rheumatoid arthritis, or repeat ocular surgeries within a short period of time may be at increased risk for corneal adverse events which may become sight threatening. Topical NSAIDs should be used with caution in these patients.

Postmarketing experience with topical NSAIDs also suggests that use more than 1 day prior to surgery or use beyond 14 days post surgery may increase patient risk for occurrence and severity of corneal adverse events.

It is recommended that NEVANAC® ophthalmic suspension be used with caution in patients with known bleeding tendencies or who are receiving other medications which may prolong bleeding time.

Information for Patients: NEVANAC® ophthalmic suspension should not be administered while wearing contact lenses.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Nepafenac has not been evaluated in long-term carcinogenicity studies. Increased chromosomal aberrations were observed in Chinese hamster ovary cells exposed *in vitro* to nepafenac suspension. Nepafenac was not mutagenic in the Ames assay or in the mouse lymphoma forward mutation assay. Oral doses up to 5,000 mg/kg did not result in an increase in the formation of micronucleated polychromatic erythrocytes *in vivo* in the mouse micronucleus assay in the bone marrow of mice.

Nepafenac did not impair fertility when administered orally to male and female rats at 3 mg/kg (approximately 90 and 380 times the plasma exposure to the parent drug, nepafenac, and the active metabolite, amfenac, respectively, at the recommended human topical ophthalmic dose).

Pregnancy: Teratogenic Effects.

Pregnancy Category C: Reproduction studies performed with nepafenac in rabbits and rats at oral doses up to 10 mg/kg/day have revealed no evidence of teratogenicity due to nepafenac, despite the induction of maternal toxicity. At this dose, the animal plasma exposure to nepafenac and amfenac was approximately 260 and 2400 times human plasma exposure at the recommended human topical ophthalmic dose for rats and 80 and 680 times human plasma exposure for rabbits, respectively. In rats, maternally toxic doses ≥10 mg/kg were associated with dystocia, increased postimplantation loss, reduced fetal weights and growth, and reduced fetal survival.

Nepafenac has been shown to cross the placental barrier in rats. There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, NEVANAC® should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Non-teratogenic Effects: Because of the known effects of prostaglandin biosynthesis inhibiting drugs on the fetal cardiovascular system (closure of the ductus arteriosus), the use of NEVANAC® ophthalmic suspension during late pregnancy should be avoided.

Nursing Mothers: NEVANAC® ophthalmic suspension is excreted in the milk of pregnant rats. It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when NEVANAC® ophthalmic suspension is administered to a nursing woman.

Pediatric Use: The safety and effectiveness of NEVANAC® in pediatric patients below the age of 10 years have not been established.

Geriatric Use: No overall differences in safety and effectiveness have been observed between elderly and younger patients.

ADVERSE REACTIONS

In controlled clinical studies, the most frequently reported ocular adverse events following cataract surgery were capsular opacity, decreased visual acuity, foreign body sensation, increased intraocular pressure, and sticky sensation. These events occurred in approximately 5 to 10% of patients.

Other ocular adverse events occurring at an incidence of approximately 1 to 5% included conjunctival edema, corneal edema, dry eye, lid margin crusting, ocular discomfort, ocular hyperemia, ocular pain, ocular pruritus, photophobia, tearing and vitreous detachment.

Some of these events may be the consequence of the cataract surgical procedure.

Nonocular adverse events reported at an incidence of 1 to 4% included headache, hypertension, nausea/vomiting, and sinusitis.

DOSAGE AND ADMINISTRATION

Shake well before use. One drop of NEVANAC® ophthalmic suspension should be applied to the affected eye(s) three-times-daily beginning 1 day prior to cataract surgery, continued on the day of surgery and through the first 2 weeks of the postoperative period.

NEVANAC® ophthalmic suspension may be administered in conjunction with other topical ophthalmic medications such as beta-blockers, carbonic anhydrase inhibitors, alpha-agonists, cycloplegics, and mydriatics.

Rx ONLY

Manufactured by:
Alcon Laboratories, Inc.
Fort Worth, TX 76134 USA
U.S. Patent No. 5,475,034

References:

1. Data on file. Alcon Laboratories, Inc. 2005.
2. Ke T-L, Graff G, Spellman JM, Yanni JM. Nepafenac, a unique nonsteroidal prodrug with potential utility in the treatment of trauma-induced ocular inflammation. II: in vitro bioactivation and permeation of external ocular barriers. *Inflammation*. 2000;24:371-384.
3. Lane SS, Modi SS, Holland EJ, et al. Nepafenac ophthalmic suspension 0.1% before and after surgery for postoperative anterior segment inflammation. Paper presented at: American Society of Cataract and Refractive Surgery; April 19, 2005; Washington, DC.
4. NEVANAC® suspension prescribing information.

Alcon®

©2005, 2007 Alcon, Inc. 06/07 NPF10500JA