What Am I Doing That Is Unapproved or off Label?

Quite a lot, thank you, and so are you!

By Michael E. Snyder, MD

A lot of what I do for my patients is off label or not approved by the FDA. That is true for all of us ophthalmologists, although some of us might not be aware of it.

A BRIEF PRIMER

The term *off label* means that we are implanting, prescribing, or otherwise using a medical product for an indication different from that approved by the FDA. When a company submits a new product to the FDA, approval is based on the studies that have been performed and submitted to the agency, and the label states the indication for which the approval was granted. Many times, the primary market to which a product is sold has little, if anything, to do with its labeling or the studies for which it was approved.

For example, no topical antibiotic is currently approved for endophthalmitis prophylaxis. Prescribing the drugs for this purpose, as I do, is off label but not illegal. Actually, it is the standard of care. Similarly, nearly all antibiotic treatments for corneal ulcers are off-label uses; only ciprofloxacin and ofloxacin are approved for this indication.

As a second example, interferon α-2b is approved for renal carcinoma but not conjunctival intraepithelial neoplasia. Topical interferon is an incredibly useful and versatile tool for the treatment of ocular surface squamous tumors with, as of yet, no documented side effects. It has a high safety profile, but its ophthalmic use is off label.

The off-label paradigm is not restricted to the prescription pad. Until the approval of trypan blue (VisionBlue; DORC International BV), we used indocyanine green (IC Green; Akorn, Inc.) to stain the anterior capsule in cases of white cataract. Most of us have now abandoned this complex dilution, although I still select indocyanine green for congenital aniridics. Their anterior capsules are thinner and more friable and can be negatively affected by trypan blue, which reduces capsular elasticity. I also find trypan blue indispensable for the capsulorhexis in pediatric eyes, since the dye (in this case favorably) reduces the elasticity of the stretchy anterior capsule (Figure 1). This indication is an untested (as far as the FDA) and off-label use of trypan blue.

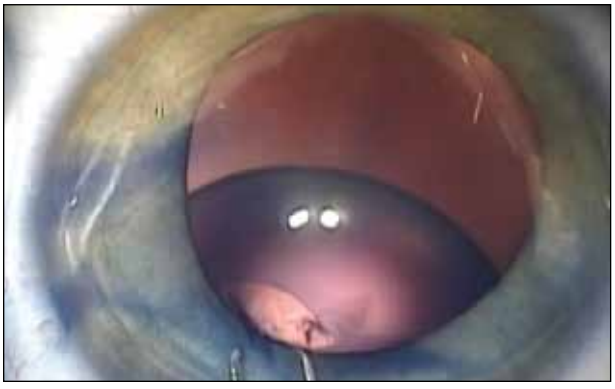

Figure 1. The surgeon uses trypan blue to reduce capsular elasticity for the capsulorhexis in the eye of a 5-year-old with Marfan syndrome.

Most, if not all, commonly used IOLs are not approved for use in children, yet we would be loathe to leave all children aphakic. I tediously counted every IOL currently approved for use with suture fixation. The final sum is … zero. Moreover, no sutures are labeled for scleral or iris fixation. In fact, my favorite for this use, polytetrafluoroethylene (Gore-Tex; W. L. Gore & Associates, Inc.) is not even labeled for ophthalmic use. Similarly, the antimetabolites 5-fluorouracil and mitomycin C (MMC) are commonly used off label in glaucoma surgery. Some surgeons also regu-

larly use MMC off label to reduce haze after PRK or as an adjunctive therapy to pterygium excision. In addition, ocular oncologists perform intravitreal injections of MMC for intraocular lymphoma, among other esoteric vitreoretinal applications, none of which carries formal FDA labeling.

The aforementioned examples are just those that came quickly to my mind.

SPECIAL CIRCUMSTANCES

Exemptions

When the FDA has not approved a product, it may not be imported, sold, or implanted except under special circumstances, which fall into two categories. The first consists of products implanted under formal FDA investigational device exemption or humanitarian device exemption studies, and the second comprises implantations under a compassionate use device exemption (CUDE). The latter requires an independent request to the FDA for permission to use a product or device on a case-by-case basis. If the exemption is granted for that particular case, careful monitoring of its use by both the clinician-investigator and an independent institutional review board is required, with follow-up information provided to the FDA. The granting of a CUDE is not an FDA imprimatur of safety. Rather, we are required to notify the patient in writing (and gain informed consent for the product's use in this setting) that the FDA has *not* tested the device for safety and that its use is investigational. Typically, the FDA will consider a CUDE when no other reasonable alternative is available.

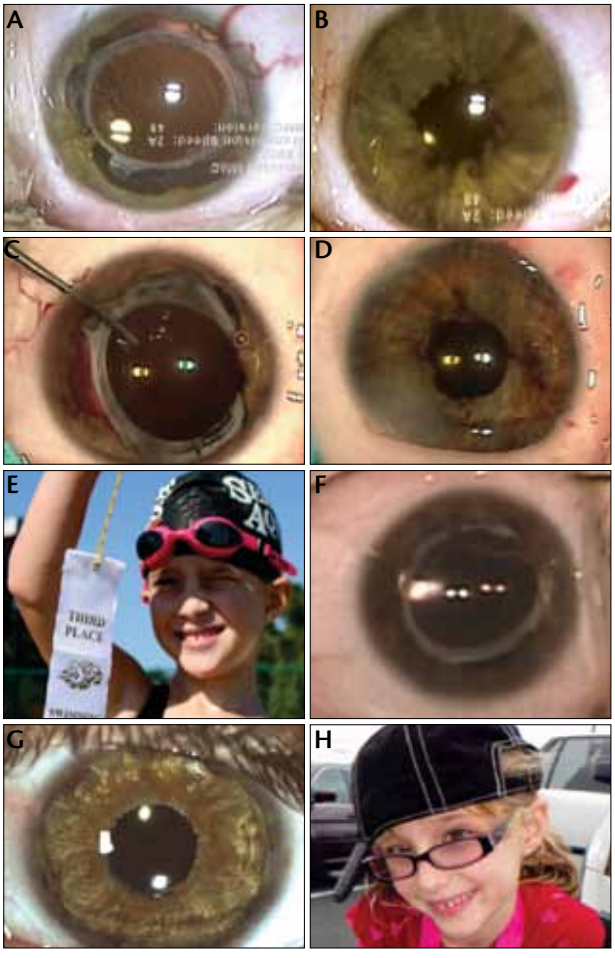

Figure 2. A newborn baby underwent multiple sphincterotomies and removal of an axial congenital cataract, resulting in severe photophobia and leaving persistent amblyopia. Presentation of the eye after the patient's referral at age 3 for iris repair (A). Appearance of eye after first repair (B), first cheese-wiring of cerclage suture (C), and second repair (D). Recurrent photophobia after second cheese-wiring. Note lid closure and shading (E). OR appearance (F). The eye after insertion of a customized iris device (G). The patient's smile returns. Note the absence of squinting and sunglasses (H).

In our practice, my colleagues and I have used the CUDE process for artificial iris cases and peculiar IOL needs. I will share two representative cases.

Example No. 1

Several years ago, a young schoolteacher presented with leukocoria in a blind eye from chronic retinal detachment.[1] She thought that her potential suitors would constantly stare at her white pupil and said that her students were frequently distracted by it, inhibiting her effectiveness in the classroom. Under a CUDE, the surgeon secured a specially made black PMMA implant in the ciliary sulcus, eliminating the leukocoria and profoundly improving the patient's self-image and self-confidence. In this case, no product existed to solve her problem, so the unique solution required was obviously not met by FDA-approved devices.

Example No. 2

A newborn baby with axial congenital cataract had been treated with multiple sphincterotomies, which not only failed to reduce her amblyopia but also left her severely photophobic (Figure 2). Although the cataract was subsequently removed, amblyopia therapy failed to progress and, further, was hindered by habitual forced lid occlusion resulting from persistent photophobia. After the failure of conservative management, at age 3, she was referred to our practice for iris repair. The surgeon performed a cerclage (purse-string suture) repair of the iris, which resolved the patient's glare symptoms and allowed some progress with amblyopia treatment. Sadly, after 2 years, the cerclage suture cheese-wired, and the photophobia returned. The surgeon performed a second suture repair with numerous imbricating sutures. The procedure relieved the patient's photophobia but again lasted only 18 months, after which intolerable symptoms

returned, resulting in both photic discomfort and a facial spasm from secondary lid closure.

Because no reasonable alternative was available, the surgeon was able to obtain a CUDE for a customized artificial iris. The implantation of a CustomFlex (HumanOptics AG) resolved the patient's glare and light sensitivity, and her smile returned.

CONCLUSION

The FDA serves an important role by protecting patients. The agency's formal approval of devices has become increasingly costly, however, and the regulatory process uncertain. Accordingly, industry only seeks the FDA's approval of devices and indications when the perceived marketplace is large enough to offset these barriers. In many instances, the proper, ethical care of patients requires the off-label use of products and, sometimes, even the use of medications and devices not approved by the FDA. It is incumbent upon us to provide effective options to our patients and to be familiar with the regulatory environments within which these options may exist. In light of the rising cost of regulatory approval, we can expect more of our care for patients with "unprofitable" diseases or conditions to fall into these categories.

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The most effective things I do fall into these categories.

By Robert K. Maloney, MD

The most effective things I do are unapproved or off label.

CATARACT SURGERY

I perform cataract surgery, a procedure that has never been approved by the FDA. Although the agency approved IOLs for use in cataract surgery, none is approved for use in IOL exchange, an important rescue procedure. At the conclusion of cataract surgery, I inject topical moxifloxacin, an off-label use, based on evidence that injecting a similar antibiotic (cefuroxime) reduces the risk of endophthalmitis.[1] The only approved use for topical moxifloxacin is the treatment of bacterial conjunctivitis, an indication of minimal benefit because the disease is self-limited. On the other hand, I find topical moxifloxacin very useful for the unapproved treatment of bacterial keratitis.

REFRACTIVE SURGERY

I regularly perform LASIK to correct refractive errors after the implantation of premium IOLs, although the procedure is not approved for patients who have undergone cataract surgery. I always use a nomogram adjustment to improve the accuracy of LASIK, but nomogram adjustments are not FDA approved. Even routine LASIK patients are, therefore, undergoing an off-label procedure in my practice. In the relatively uncommon instance when one of my patients requires a LASIK enhancement, I do not hesitate to proceed, even though retreatments are unapproved.

Preoperatively, I measure patients' manifest refraction—an unapproved procedure. Nor is the phoropter an approved device. I also examine patients' eyes at the slit lamp, another unapproved device. I assess the fundus with an indirect ophthalmoscope, the safety and effectiveness of which have never been demonstrated to the FDA's satisfaction.

COMMUNICATION

Many medical procedures are not approved by the FDA, including appendectomy, coronary artery bypass graft, excision of a lung tumor, removal of an intracranial meningioma, and splinting of a broken limb. Unfortunately, it is more difficult than it should be to obtain information about highly effective, unapproved procedures, because companies are not allowed to communicate this information to physicians. Companies that do risk hefty fines. Communication between physicians is now regulated by the continuing medical education authorities, so a free exchange of ideas is no longer possible at most meetings.

This brings me to the unapproved procedure that I perform most often: talking to patients. Of course, discussions with patients of all their options have not yet been proven safe and effective. How long will it be before I am forbidden to talk about unapproved treatments like an IOL exchange or splinting a fracture?

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We are using cyanoacrylate glue in ophthalmology.


By Derek W. DelMonte, MD, and Terry Kim, MD

Cyanoacrylate and related compounds are fast-acting adhesives that have been used for everything from model airplane construction to dental repair. Initially discovered by researchers trying to find a suitable, clear, gun sight plastic in the 1940s, cyanoacrylate's utility as a "super glue" became evident, and it was made commercially by the Kodak company under the name Eastman 910 soon thereafter.[1] Although cyanoacrylate glues were reportedly used in the Vietnam War to retard bleeding in wounded soldiers, they were not officially approved by the FDA for human use until 1998 with the release of Dermabond (Ethicon, Inc.).[2] Despite the adhesives' success for the treatment of many ailments involving just about every part of the human body, their use remains off label in ophthalmology. Nevertheless, surgeons use cyanoacrylate glue as an office-based artificial corneal patch graft for patients with corneal melts (Figure 1), perforations, or wound leaks; to close the skin in oculoplastic procedures; as a temporary tarsorrhaphy in exposure keratopathy; and to facilitate occlusive therapy for amblyopia.

WHY GLUE?

Cyanoacrylate glue may be useful for eyes with corneal disorders in the acute setting. For example, quickly patching an area of bare corneal stroma prior to re-epithelialization may prevent the production of additional collagenase at the site of melting corneal stroma.[3] In cases of infectious perforation, delaying the need for a penetrating keratoplasty can allow significantly more time for anti-infectious therapies to be effective, thereby increasing the chance of success of a future corneal graft (Figure 2). Because cyanoacrylate glues also have an intrinsic bacteriostatic activity against gram-positive organisms, they help create a barrier against the intraocular extension of some infections.[4]

In some instances of an acute penetrating injury, sealing the perforation with glue can eliminate the need for future surgical intervention. Particularly with small, clean penetrating injuries, the corneal stroma can heal under the hardened glue and eventually shed the patch, leaving an intact, healed cornea in its place. Moreover, in patients with a corneal perforation who are difficult to bring to the OR for other medical reasons, closing the eye with cyanoacrylate glue will help prevent endophthalmitis, significantly improving the eye's long-term prognosis.

Figure 1. A 45-year-old man with an acute corneal melt due to infectious keratitis (*Pseudomonas*).

Figure 2. Closing the area of melting with cyanoacrylate glue permitted antibiotics to quiet the eye, which allowed a more controlled surgical intervention that successfully restored excellent vision to this patient.

Despite their value in corneal patching, cyanoacrylate glues are not acceptable for scleral applications. A severe inflammatory reaction incited by the glue was found to inhibit collagen remodeling in several studies.[5]

APPLICATION

Cyanoacrylate glues can be successfully applied in many different ways. The direct application of these adhesives to the bed of a thinning ulcer, with or without an overlying amniotic membrane or biologic patch graft, effectively prevents progressive thinning. This technique is useful in patients with various ulcerative disorders, including autoimmune stromal melts, chemical burns, neurotrophic ulcers, and radiation keratitis.[6] Some surgeons also place a bandage contact lens over the treated area in an attempt to seal the lens to the ocular surface and increase protection of the area as it heals. Keeping a contact lens in place long term, however, increases the risk of infection.

In our practice, we have found that less is more when using cyanoacrylate glue for corneal pathology. By directly

applying a very thin layer of glue to the base of an ulcer, we can safely seal the area while avoiding a large, irregularly elevated "glue foreign body," which can be uncomfortable for the patient and can damage the surrounding anatomy. An overlying bandage contact lens can increase the patient's comfort and prevent movement of the eyelids from dislodging the glue prematurely. When we use bandage contact lenses, we try to avoid its adhesion with glue so that we may change the lens as necessary to help avoid the infectious complications of long-term wear. Given the favorable safety profile of this therapy, we generally attempt to glue all melting ulcers and perforations prior to surgical planning. We find that this measure allows us additional time for determining future intervention, thereby increasing our chances of successful long-term outcomes.

ADVANTAGES OF CYANOACRYLATE OVER OTHER ADHESIVES

Although other adhesives have been developed since the first use of cyanoacrylate, most notably biologic adhesives such as two-part fibrin-based glue, cyanoacrylate retains many advantages. It does not require a complex preparatory process and can be used quickly in an office setting. It is far less expensive than newer biologic adhesives. Finally, cyanoacrylate adhesives do not require refrigeration or other special conditions for storage, which makes them ideal for emergency departments or office-based practices. These advantages make cyanoacrylate an effective and efficient office-based treatment modality for perforated or thinning corneas.

Nonetheless, cyanoacrylate glue carries several limitations, including a brittle, hard consistency, an opaque nature, and an ability to incite corneal inflammation and neovascularization. We hope that adhesives or sealants under development specifically for ophthalmic use will represent significant improvements over both cyanoacrylate glue and current biologic adhesives.

CONCLUSION

Cyanoacrylate glues have become an important part of our corneal practice and will continue to be for the foreseeable future. With proper use, cyanoacrylate glues can be a safe and effective alternative to emergency surgery, and they can greatly improve the long-term prognosis of many eyes.

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We administer intracameral steroids and antibiotics at the conclusion of cataract surgery.


By George O. Waring IV, MD, and Luis E. Fernández de Castro, MD

At approximately 3 million procedures annually, cataract surgery is one of the most commonly performed surgeries in the United States.[1] The success of many medical treatments relies on the correct use of drugs with respect to dosage, frequency, continuity, and compliance. Between 30% and 60% of patients with illnesses do not adhere to prescribed medical therapy, however, which can lead to adverse effects and disease progression.[2] Improving surgical outcomes and minimizing recovery time are the keys to satisfied patients and a successful medical practice. Intracameral prophylactic medications are one method for making cataract surgery simpler and potentially safer.

ANTIBIOTICS

Infectious postoperative endophthalmitis is a rare but catastrophic complication of intraocular surgery. Its incidence after cataract surgery is approximately 0.07%.[3] Although ophthalmologists' use of intracameral antibiotic prophylaxis for the prevention of endophthalmitis in cataract surgery is controversial, the

practice is supported by a growing body of evidence. The results of the European Society of Cataract and Refractive Surgeons' endophthalmitis study suggested that patients who received intracameral cefuroxime had a lower incidence of endophthalmitis than those who did not or who received topical antibiotics.[4,5]

The ideal intracameral antibiotic agent would be broad spectrum, bactericidal, fast acting, and nontoxic. Fourth-generation fluoroquinolones have been used in pre- and postoperative topical antibiotic regimens for cataract surgery because of their broad spectrum of action as well as their overall safety and tolerance by vital intraocular tissues. Commonly used intracameral antibiotics include vancomycin, moxifloxacin, and cefuroxime. Moxifloxacin 0.5% ophthalmic solution has a broad spectrum of antimicrobial action, is readily available, and is preservative free. For these reasons, we routinely perform an intracameral injection of preservative-free moxifloxacin after routine and complex cataract surgery. Because aqueous turnover is swift, we supplement the drug's use with the topical administration of a commercially available preparation of topical moxifloxacin.

STEROIDS

Ophthalmologists have used steroids topically and subconjunctivally to treat inflammation after cataract surgery. Although effective for this purpose, the topical agents have several disadvantages, including the requirement of the patient's compliance with prescribed dosing, cost, and exposure of the ocular surface to preservatives. Despite a report that the concentration of intravitreally injected triamcinolone acetonide in aqueous humor is nontoxic,[6] surgeons still have concerns about the intracameral use of steroids. It is not uncommon for residual triamcinolone to resemble anterior chamber cell and/or hypopyon during the early postoperative period. The drug can be distinguished from toxic anterior segment syndrome or infectious endophthalmitis, however, by the absence of fibrin, injection, pain, corneal edema, and other signs and symptoms associated with more sinister conditions.

We do not routinely use intracameral triamcinolone in patients with high-risk glaucoma or known steroid responders due to the risk of a steroid response. We do, however, feel its use is important for quelling postoperative inflammation in cases of combined phacoemulsification and endocyclophotocoagulation. We supplement this therapy with topical steroids as needed and treat postoperative elevations in IOP in the usual fashion.

Although further studies are needed, theoretically, the intracameral injection of triamcinolone may decrease the incidence of postoperative cystoid macular edema. In the event of vitreous presentation, the drug improves the strands' visibility for assessment and subsequent management. Additional benefits of preservative-free intracameral triamcinolone acetonide are that it renders patients' compliance a nonissue, it is cost-effective, and it generally produces quiet eyes with minimal postoperative inflammation.

A preservative-free, pre-prepared mixture of intracameral moxifloxacin and triamcinolone acetonide can be ordered from a compounding pharmacy. We routinely inject this solution at the end of the case, with the cannula's tip placed under the iris to encourage posterior penetration. It is important to advise patients and their families that the milky suspension can temporarily blur vision on the postoperative day but that this side effect will gradually resolve.

CONCLUSION

Intracameral prophylactic therapy at the conclusion of cataract surgery appears to be a low-risk procedure. Injections spare patients the cost of a postoperative medication and reduce the number of drops they must remember to instill. Further studies are needed, however, to evaluate the safety and efficacy of intracameral prophylactic therapy for routine and complex cataract surgery. ■

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