Fundamentals of Fluorescein Angiography

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LEARNING OBJECTIVES:

1. Identify the physical phenomenon of fluorescence and its uses in ophthalmic photography.
2. Discuss common adverse reactions and possible interventions during angiography.
3. List three conditions for which fluorescein angiography may help determine therapy/treatment.

SUCCESSFUL COMPLETION

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Since its introduction in the early 1960s, fluorescein angiography has proved to be an essential tool for diagnosis of many retinal disorders. Fluorescein sodium fluoresces when exposed to blue light at wavelengths between 465 and 490 nm. Fluorescence occurs at the yellow-green wavelengths of 520 to 530 nm. The most common uses of fluorescein angiography are in retinal or choroidal vascular diseases such as diabetic retinopathy and macular degeneration. Fluorescein angiography is performed by injecting fluorescein sodium dye as a bolus into a peripheral vein. The normal adult dosage is 500 mg. Side effects include temporary discoloration of the skin and urine. Fluorescein sodium is well tolerated by most patients, but angiography is an invasive procedure with an associated risk of complications or adverse reactions. Adverse reactions occur in 5%–10% of patients and range from mild to severe. Life-threatening reactions are rare, but clinical personnel should be properly equipped and prepared to manage serious reactions.

Fundamentals of Fluorescein Angiography

Ophthalmic photography has at times seemed almost synonymous with fluorescein angiography. Since its introduction in the early 1960s, fluorescein angiography has become an essential tool in the understanding, diagnosis, and treatment of retinal

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disorders. This diagnostic procedure utilizes a specialized fundus camera or scanning laser ophthalmoscope to capture rapid-sequence photographs of the retina following an intravenous injection of fluorescein sodium. Photographic or video images taken as the dye courses through the eye can demonstrate abnormalities within the neurosensory retina, pigment epithelium, sclera, choroid, and optic nerve, providing clinically useful information for nearly the entire spectrum of posterior segment disorders.

Fluorescence

Fluorescein angiography is an application of the physical phenomenon of fluorescence (Wolfe, 1986). Fluorescence is a type of photoluminescence that occurs when susceptible molecules known as fluorophores absorb electromagnetic energy, temporarily exciting them to a higher energy state. As the molecules return to their original energy level, they emit light of a different, usually longer wavelength. Unlike phosphorescence, which continues to occur after the excitation source is removed, fluorescence requires continuous excitation. Once the excitation source is removed, emission of fluorescence stops almost immediately (10^{-8} seconds).

Fluorescence occurs naturally in certain compounds and may occasionally be observed in the human eye. Optic nerve drusen, astrocytic hamartomas, lipofuscin pigments in the retina, and the aging human lens are all believed to exhibit natural fluorescence that can be documented with photographic techniques.

Fluorescein Sodium

Although commonly referred to as fluorescein, the dye used for fluorescein angiography is actually fluorescein sodium ($C_{20}H_{10}Na_2O_5$). It is the water-soluble salt of fluorescein, also known as resorcinol phthalein sodium, or uranine (Morris, 2002). A member of the xanthene group of dyes, fluorescein sodium is a highly fluorescent chemical compound synthesized from the petroleum derivatives resorcinol and phthalic anhydride (Jacobs, 1992). The dye was first synthesized in 1871 by Adolf von Baeyer, who later received the 1905 Nobel Prize in Chemistry for his work in organic dyes.

Fluorescein sodium absorbs blue light, with peak excitation occurring at wavelengths between 465 and 490 nm. The resulting fluorescence occurs at the yellow-green wavelengths of 520 to 530 nm (see Figure 1). Dye concentration and pH can affect the intensity of fluorescence. Maximum fluorescence occurs at a pH of 7.4, but the pH of fluorescein sodium for angiographic use is adjusted to a range of 8.0 to 9.8 for stability. In powdered or concentrated solution form, fluorescein sodium appears orange-red in color. Fluorescence is detectable in concentrations between 0.1% and 0.0000001%. In broad-spectrum illumination, diluted fluorescein sodium appears bright yellow-green in color. When illuminated with blue light, the yellow-green color intensifies dramatically.

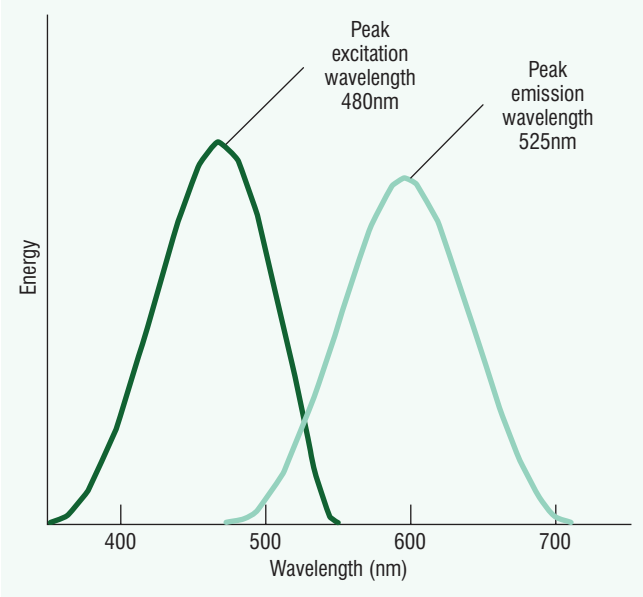

Figure 1. Excitation and emission characteristics of fluorescein.

The fluorescent properties of this dye have made it in useful in a variety of industrial, scientific, military, and medical applications. Fluorescein sodium was the first fluorescent dye used for water-tracing purposes (Dole, 1906). It has been used as a visible marker for search-and-rescue operations and to track and measure flow dynamics of water sources, map subterranean water courses, track hazardous spill dispersion patterns, identify point sources of pollution, and detect leaks or obstructions in plumbing and sewage systems. In fact, its common use in industrial plumbing led a plumbers union to start the tradition of using fluorescein to stain the Chicago River green for the annual St. Patrick's Day celebration.

Many of the medical and ophthalmic applications of fluorescein are analogous to its uses in plumbing or industrial flow dynamics. For example, it has been used for intraoperative assessment of blood flow in surgical resections and grafts with a Wood's light to excite fluorescence (Myers, 1962; McCaw, Myers, & Shanklin, 1977; Marfuggi & Greenspan, 1981). In ophthalmology, topical application of fluorescein sodium is routinely used for applanation tonometry and as a vital stain in the documentation of ocular surface disorders such as corneal ulcers, abrasions, or other epithelial defects (Martonyi, Bahn, & Meyer, 1985). It is sometimes

used to determine tear film breakdown time, check the fit of contact lenses, verify the patency of lacrimal passageways, and detect leakage of aqueous humor from corneal or conjunctival wounds using the Seidel test (see Figure 2).

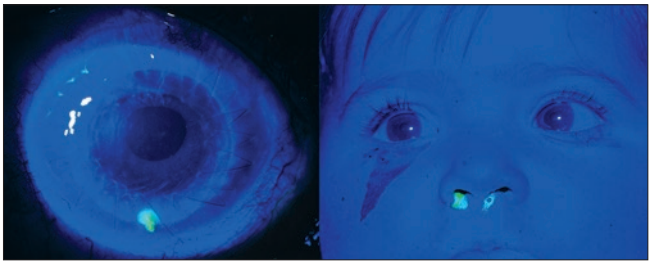

Figure 2. Left: Corneal transplant wound leak identified with topical fluorescein. Right: Fluorescein dye disappearance test can be used to assess nasolacrimal duct obstruction.

Indications and Uses

Fluorescein angiography provides valuable diagnostic information in a number ocular conditions (see Table 1). The most common uses of fluorescein angiography are in retinal or choroidal vascular diseases such as diabetic retinopathy, age-related macular degeneration, hypertensive retinopathy and vascular occlusions (see Figure 3). Typically, these are clinical diagnoses and the angiogram is used to determine the extent of damage, to develop a treatment plan or to monitor the results of treatment. In diabetic retinopathy the angiogram is useful in identifying the extent of ischemia, the location of microaneurysms, the presence of neovascularization, and the extent of macular edema. In age-related macular degeneration, angiography is useful in identifying the presence, location and characteristic features of choroidal neovascularization for possible treatment with laser photocoagulation, photodynamic therapy, or antiangiogenic medications.

Fluorescein angiography can be very useful in certain degenerative and inflammatory conditions. Some of these conditions exhibit characteristic fluorescence patterns, which support the diagnosis. For example, Stargardt disease exhibits a "silent choroid" and a central bulls-eye fluorescence pattern in the macula, while acute posterior multifocal placoid pigment epitheliopathy (APMPPE) demonstrates a characteristic "block early, stain late" pattern (see Figure 4).

TABLE 1

Complications and Adverse Reactions

- Extravasation of dye
- Transient nausea
- Vomiting
- Pruritis
- Urticaria
- Bronchospasm
- Laryngeal edema
- Anaphylaxis
- Hypotension
- Syncope
- Seizures
- Myocardial infarction
- Cardiac arrest

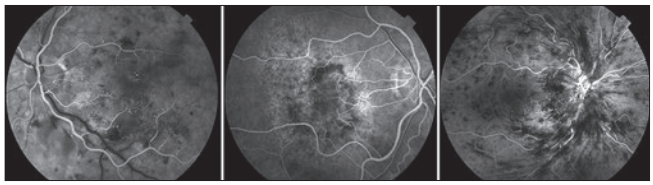

Figure 3. Left: Diabetic retinopathy. Middle: Age-related macular degeneration. Right: Central retinal vein occlusion.

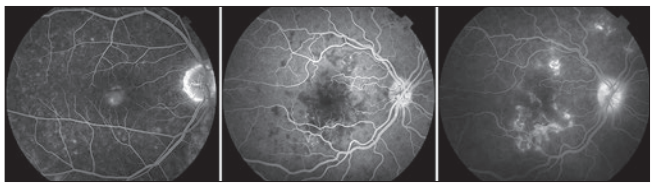

Figure 4. Left: "Silent choroid" in Stargardt disease. Middle: APMPPE lesions block fluorescence early in the study. Right: AMPPE lesions stain with fluorescein later in the series.

Angiography also plays an important role in clinical research, advancing the understanding of retinal vascular disorders and potential treatment modalities. A number of multicenter clinical trials use fluorescein angiography to investigate new treatment options to combat retinal disease. As new therapeutic modalities are developed, fluorescein angiography will continue to play an important role in the management of common retinal conditions.

Dosage and Administration

Fluorescein angiography is performed by injecting fluorescein sodium dye as a bolus into a peripheral vein (see Figure 5). The normal adult dosage of 500 mg is typically packaged in doses of 5 ml of 10% or 2 ml of 25%. For pediatric patients, the dose is adjusted to 35 mg per 10 pounds of body weight. Upon entering the circulation, approximately 80% of the dye molecules bind to plasma proteins, which significantly reduce fluorescence because the free electrons that form this chemical bond are subsequently unavailable for excitation (Wolfe, 1986). The remaining unbound or free fluorescein molecules fluoresce when excited with light of the appropriate wavelength. With a molecular weight of 376,

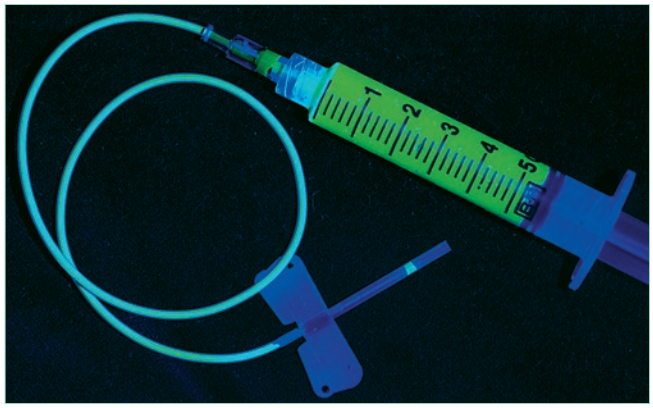

Figure 5. Fluorescein diluted with saline to demonstrate the characteristic fluorescent green appearance under blue excitation light.

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fluorescein diffuses freely out of all capillaries except those of the central nervous system, including the retina.

The dye is metabolized by the kidneys and is eliminated through the urine within 24 to 36 hours of administration. During this period of metabolism and elimination, fluorescein has the potential to interfere with clinical laboratory tests that use fluorescence as a diagnostic marker (Palestine, 1991; Bloom, Herman, & Elin, 1989). To avoid any false readings, it may be prudent to either schedule clinical lab tests before the angiogram or postpone testing for a day or two to allow for sufficient elimination of the dye. Side effects of intravenous fluorescein include discoloration of the urine for 24 to 36 hours and a slight yellow skin discoloration that fades within a few hours. Nursing mothers should be cautioned that fluorescein is also excreted in human milk (Mattern & Mayer 1990).

Complications and Adverse Reactions

Fluorescein sodium is well tolerated by most patients, but angiography is an invasive procedure with an associated risk of complication or adverse reaction (see Table 2). Use of fluorescein sodium may be contraindicated in patients with history of allergic hypersensitivity to fluorescein. Although generally considered safe for patients receiving dialysis, one manufacturer of fluorescein suggests using half the normal dose in dialyzed patients (Akorn, Inc., 2005). There are no known risks or adverse reactions associated with pregnancy, but most practitioners avoid performing fluorescein angiography in pregnant women, especially in their first trimester (Halperin, Olk, Soubrane, & Coscas, 1990; Greenberg & Lewis 1991; Berkow, Flower, Orth, & Kelley, 1997).

TABLE 2

Common Diagnostic Uses and Indications for Fluorescein Angiography

- Diabetic retinopathy
- Age-related macular degeneration
- Subretinal neovascular membrane from other causes (myopia, histoplasmosis, etc.)
- Central retinal vein occlusion
- Branch retinal vein occlusion
- Central serous chorioretinopathy
- Cystoid macular edema
- Hypertensive retinopathy
- Central retinal artery occlusion
- Branch retinal artery occlusion
- Retinal arterial macroaneurysms
- Pattern dystrophies of the retinal pigment epithelium
- Choroidal tumors
- Chorioretinal inflammatory conditions
- Hereditary retinal dystrophies

Historically, adverse reactions occur in 5%-10% of patients and range from mild to severe (Chazan, Balodimos, & Koncz, et al., 1971; Pacirariu, 1982; Butner & McPherson, 1983; Marcus, Bovino, & Williams, 1984; Yannuzzi et al., 1986; Karhunen, Raitta, & Kala, 1986; Kwiterovitch, et al., 1991). Anecdotal evidence suggests a lower incidence of reaction in recent years, and the first large study conducted in over a decade seems to confirm this, reporting a frequency of adverse reaction of just over 1% (Kwan, Barry, McAllister, & Constable, 2006). Continued improvements in manufacturing processes and implementation of tighter pharmacopeial standards are credited with this reduction and may lead to lower rates of reaction in the future (Eutick, 2006).

Transient nausea and occasional vomiting are the most common reactions and require no treatment. These mild reactions typically occur 30–60 seconds after injection and last for about one to two minutes. Fortunately, they seldom compromise the diagnostic quality of the angiogram. The incidence of nausea and vomiting seems to be related to the volume of dye and rate of injection. A relatively slow rate of injection often reduces or eliminates this type of reaction but can adversely affect image quality and alter arm-to-retina circulation times. Premedication with promethazine hydrochloride or prochlorperazine may prevent or lessen the severity of nausea and vomiting in patients with a history of previous reactions to fluorescein. However, such premedication is rarely needed, and one study noted a higher frequency of these reactions in patients who had been premedicated (Yannuzzi et al., 1986). Some patients report a strong taste sensation or hypersalivation following injection of fluorescein.

Moderate reactions occur less frequently, affecting less than 2% of patients who undergo angiography. Allergic reactions such as pruritus or urticaria can be treated with antihistamines, but any patient who experiences these symptoms should be observed carefully for the possible development of anaphylaxis. The advisability of performing angiograms in patients with a history of allergic reaction to fluorescein should be considered carefully, as allergic sensitization to the dye can increase with each subsequent use. Patients with previous history of mild allergic reaction to fluorescein can be pretreated with an antihistamine, such as diphenhydramine, 30–40 minutes prior to any subsequent angiograms to limit allergic response, although this may not prevent serious reactions (Ellis, Schoenberger, & Rendi, 1980). Vasovagal attacks happen in some patients, most likely due to anxiety about the procedure or their ocular condition (Buchanan & Levine, 1982). Usually in these cases the angiogram needs to be aborted or postponed, but some patients are able to tolerate

the angiogram during the initial stages of a syncopal episode. However, the drop in blood pressure and heart rate can dramatically alter the angiographic results (Merin & Lam, 1994).

More severe reactions, which are rare, include laryngeal edema, bronchospasm, anaphylaxis, tonic-clonic seizure, myocardial infarction, and cardiac arrest (Gombos & Lieberman, 1989; Kelly, McDermott, Saunders, & Leach, 1989; Hess & Pacirariu, 1976; Deglin, S. M., Deglin, E. A., & Chung, 1977; Ascaso et al., 1993). The overall risk of death from fluorescein angiography has been reported as 1 in 222,000 (Yannuzzi et al., 1986). Although life-threatening reactions during angiography are rare, angiographic facilities and personnel should be properly equipped and prepared to manage serious reactions to the procedure. A resuscitative crash cart and appropriate agents to treat severe reactions should be readily available, including epinephrine for intravenous or intramuscular use, soluble corticosteroids, aminophylline for intravenous use, oxygen, and airway instrumentation. It is generally recommended that a physician be present or available during angiographic procedures.

Team Implications

Pre-Procedure

Diagnostic facilities in ophthalmic specialty clinics and hospitals adapt protocols for fluorescein angiography (FA) procedure. Foremost, a request for FA must be signed by the ordering physician (ophthalmologist) as fluorescein is considered a drug (Watkinson & Scott, 2002). Secondly, as FA is an invasive procedure, the consent for the procedure must be reviewed to ensure it has been fully explained and understood by the patient. Additionally, the patient's medical history should be reviewed including drug and food allergies, asthma, renal insufficiency, diabetes mellitus, cardiac diseases, possibility of pregnancy, current prescribed medications and creatinine level result (Prall, Shah, & Kim, 2015 & Watkinson & Scott, 2002). Allergy to fluorescein dye is considered a contraindication to use, but some physicians elect to perform angiography after premedication with antihistamines in patients with previous history of mild allergic reactions (AAO, n. d.). Patients who are allergic to sulfa drugs and seafood, and diabetic patients on metformin, are particularly singled out for indocyanine green angiography as it contains iodine and may precipitate severe allergic reactions and lactic acidosis, respectively, but this is not a concern in fluorescein angiography (Nawaz, Cleveland, Gaines, & Chan, 1998). Ophthalmic team members ensure that emergency equipment (e.g., code cart) is readily available in the event of an adverse reaction during or after the procedure.

The patient's visual acuity must be checked and charted along with the slit-lamp, funduscopic, and other ocular findings. The refractive media such as the lens and cornea, and the vitreous should be clear to facilitate the best view of the retina. Dilating agents like 1% tropicamide and 2.5% phenylephrine eye drops are instilled 20 to 30 minutes prior to the procedure (Prall, Shah, & Kim, 2015; & Watkinson & Scott, 2002). Insertion of a butterfly infusion set using a 21 or 23 gauge needle attached to a 3" or 12" tubing connector with a stopcock should be started in the antecubital vein and checked for patency.

During the Procedure

Education about what the patient can expect during the procedure will facilitate patient cooperation. The patient needs to be instructed to keep still as he/she will be seated similar to having a slit-lamp examination with the chin on the chin rest and the forehead against the support bar to keep the head from moving while the ophthalmic photographer takes pictures of the retina through the dilated pupil (Watkinson & Scott, 2002).

The team member administering the dye should check the syringe for lack of air prior to injection to prevent air embolism. After the ophthalmic photographer takes initial pictures of the retina, the patient is informed about the rapid push of 5 ml of 10% (or 2ml of 25%) of fluorescein intravenously. If the patient complains of pain during the injection, it is immediately stopped. In cases of extravasation, the antecubital vein is taped to prevent tissue ulceration and ice pack is applied to the area to induce vasoconstriction (Watkinson & Scott, 2002).

Fluorescein normally reaches the retina in seconds (Prall, Shah, & Kim, 2015). Upon injection into an antecubital vein dye passes through short posterior ciliary arteries and reaches the optic nerve and choroid within 8–12 seconds. The early arteriovenous phase of the filling of the retinal arteries, arterioles and the capillaries is followed by the late arteriovenous phase or laminar venous phase. The phase with maximal fluorescence occurs at 30–60 seconds followed by the recirculation phase. After 10 minutes, the appearance of fluorescein is diminished in the retinal vessels but the optic nerve head, sclera, and Bruch's membrane can still be stained with fluorescein and continue to fluoresce (Prall, Shah, & Kim, 2015).

Post-Procedure

After the procedure the ophthalmic team monitors vital signs and potential signs of shock or allergic reaction every 5 minutes for 20 minutes. Most adverse reactions occur within 20 minutes of fluorescein administration, hence the monitoring for a minimum of 20 minutes after injection of the dye. Close monitoring and proximity of the physician is critical in the event acute adverse reactions need to be diagnosed and managed (Prall, Shah, &

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Kim, 2015). Intravenous access can be discontinued after it is determined the patient is stable.

Ophthalmic team members provide post-procedure education, informing the patient of the following:

- He/she may see blue, red after-images for several minutes after the procedure;
- Dilated pupils may cause difficulty with focusing, causing blurriness especially when reading for 3 to 4 hours;
- Sunglasses may be used to manage glare;
- Urine and/or skin discoloration often disappears after 24 hours;
- Drink plenty of water to flush dye out of the body;
- Another person will need to drive the patient home; and,
- Follow-up appointments and office contact numbers for notification of concerns (Watkinson & Scott, 2002).

Extravasation of fluorescein dye during the injection can be a serious complication of angiography. With a pH of 8.0 to 9.8, fluorescein infiltration can be quite painful. If fluorescein dye extravasates, cold compresses should be placed on the affected area for 5 to 10 minutes, and the patient should be reassessed until edema, pain, and redness resolve. Serious complications are more likely to occur when large amounts of dye extravasate. Sloughing of the skin, localized necrosis, subcutaneous granuloma, and toxic neuritis have been reported following extravasation of fluorescein (Schatz, 1978; Elman et al., 1987; Lipson & Yannuzzi, 1989). To avoid these problems, continual observation of the injection site during the course of the injection and monitoring the patient for pain are recommended. Although rare, accidental arterial injections can be quite painful (see Figure 6). The dye remains concentrated and stains the effected extremity, with little or no dye reaching the retinal vasculature. With proper technique, these complications of injection can usually be avoided.

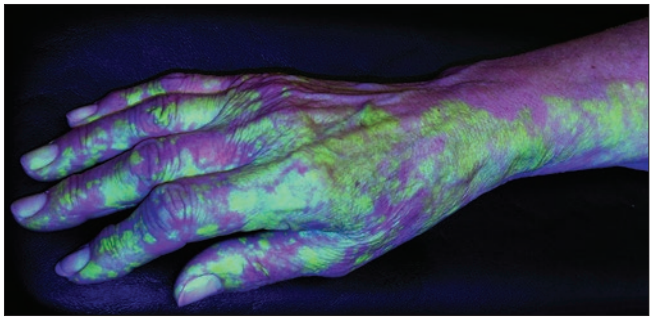

Figure 6. Accidental arterial injection. Note localized tissue staining under blue excitation light.

In cases when venous access is severely compromised or the patient is known to be highly allergic to the dye, fluorescein can be administered orally (Kelley & Kincaid, 1979; Hara, T., Inami, & Hara, T., 1998). Although oral fluorescein administration is typically well tolerated, severe adverse reactions can occur (Kinsella & Mooney, 1988; Gomez-Ulla, Gutierrez, & Seonae, 1991). Due to the slow absorption rate, an early transit sequence is not possible. The resulting images are less than ideal but have traditionally provided limited diagnostic information in conditions where late phase photographs are helpful, such as cystoid macular edema. The use of optical coherence tomography to detect the presence of edema or fluid within the retinal tissues has essentially eliminated this use of oral fluorescein.

Summary

In order to provide safe patient care during fluorescein angiography, it is critical that ophthalmic team members understand the use of fluorescein for diagnosing eye-related diseases and conditions, including appropriate doses for adult and pediatric patients. Awareness of side effects, adverse reactions, and complications of the contrast agent allow the ophthalmic health-care team to anticipate, respond quickly, and support the patient during and following the angiographic procedure using fluorescein.

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