LETTERS TO THE EDITOR

**Fluorescein Concentrations in Human Breast Milk**

In the past few months there have been discussions—online and elsewhere—regarding fluorescein elimination in breast milk and recommendations for lactating patients undergoing fluorescein angiography. The desire to perform fluorescein angiography on postpartum women raised concerns regarding safety to the nursing infant and it was unknown if women should refrain from nursing following fluorescein injection. Life-threatening phototoxicity secondary to fluorescein administration has been described in a premature infant. In 1991, we conducted a study to ascertain the concentration of fluorescein eliminated in breast milk over an extended period of time. The results of this study were presented that year at the Association for Research in Vision and Ophthalmology (ARVO). The study was performed on a woman who was 8 months postpartum. Nursing was curtailed for the first 8 hours of the study. The woman received 5 cc of 10% fluorescein sodium intravenously. Bilateral simultaneous electric pump expression of breast milk with complete emptying at each time point was performed at 1, 2, 4, 8, 30, 96, and 120 hours after fluorescein administration. Each sample was dated and stored in individual containers in a below zero degree Celsius freezer. Fluorescein concentrations in breast milk samples were determined using a scanning fluorophotometer with a sensitivity of 1 ng/ml. The concentration of fluorescein measured in the breast milk specimens ranged from a peak concentration of 826 ng/ml in the earliest sample to 391 ng/ml. The half-life of fluorescein elimination in breast milk was approximately 3 hours.

Our results demonstrated the early appearance of fluorescein in breast milk one hour after intravenous administration and prolonged elimination with readily detectable levels 5 days after injection. Without measuring the concentration of fluorescein in the blood or urine of a nursing infant, it is difficult to determine the actual amount of absorption by the infant. The impaired hepatic and renal function in a premature infant could lead to a cumulative dose of fluorescein from breast milk which may approach toxic concentrations. Based on our results, it seems prudent that lactating women undergoing intravenous fluorescein administration should be advised to refrain from nursing for at least 8-12 hours post-injection and possibly for longer periods with premature infants.

If the fluorescein angiogram can be safely delayed, an adequate supply of breast milk could be expressed and stored for post-angiogram feedings. For information regarding proper storage of breast milk, access www.aap.org or www.breastfeeding.net* for the American Academy of Pediatrics web site.

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**References:**

**Key Words:**
Fluorescein sodium, human breast milk.

**Does orally administered sodium fluorescein assist in the diagnosis of age related macula degeneration?**

Two recent reports in the *Journal of Ophthalmic Photography* have described the benefit of orally administered sodium fluorescein patients where intravenous injection was impractical. It was noted that fluorescein angiography is used to document three features: approximate circulation velocity, documentation of anatomic detail and the integrity of the blood retinal barriers. Also noted was that rapid intravenous dye injection is not required to evaluate the physiologic barriers of the retinal pigment epithelium and the retinal vascular endothelium. Following these descriptions, orally administered sodium fluorescein was used to perform an angiogram with a patient where repeat attempts at venipuncture could not obtain a successful cannulation. The case history is presented along with the angiographic findings. Interpretation of the results to determine if there was an underlying choroidal neovascular membrane remained inconclusive. It is therefore of interest to survey opinion of the readership to determine other members experiences with the efficacy of oral fluorescein in age related macula degeneration (ARMD).

This 80 year old male presented with corrected visual acuities of 20/200 right and 20/40 left. Fundal exami-
nation showed marked, advanced atrophic ARMD in the right eye and multiple soft drusen and atrophic changes in the left macula. His left central vision had become blurred over several months and he was referred for fluorescein angiography to eliminate the possibility of a choroidal neovascular membrane. Previous medical history consisted of cardiovascular disease, angioplasty and a pacemaker. Several unsuccessful attempts were made to cannulate a vein with increasing agitation from the patient. It was decided to attempt an orally administered fluorescein angiogram. 10 millilitres of 10% sodium fluorescein dissolved in 250 millilitres of orange juice and this “cocktail” was taken with equanimity by the patient.

Retinal photographs were taken at 30, 45 and 60 minutes post ingestion using a Zeiss FF4 fundus camera. Although a poor quality angiogram was recorded, sufficient detail could be visualized from the negatives in the left eye to determine that there were multiple window defects around the macula and what appeared to be a small amount of central fluid at all three photographic time frames. Figures 1 and 2 are prints from the angiogram at 30 and 60 minutes respectively. No treatment was administered as the results were considered to give insufficient information to warrant laser photocoagulation.

This, therefore raises two points:

1. Is orally ingested sodium fluorescein a practical alternative in the diagnosis of ARMD?
2. How would other, more experienced, colleagues interpret these results and how many have experience with oral fluorescein angiograms with ARMD?

This was considered an interesting case which raised the question of whether oral ingestion of fluorescein was a viable alternative in patients with ARMD. I would appreciate comments and opinions of these results so that if this situation arises again in the future the potential, projected outcome of an oral fluorescein can be decided on the basis of informed opinion from this experienced forum.

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KEY WORDS:
oral fluorescein, age related macular degeneration

Is ICG choroidal angiography safe for diabetic patients taking metformin?

Recently there has been some controversy among ophthalmic photographers regarding the safety of indocyanine green (ICG) choroidal angiography in diabetic patients taking the hypoglycemic drug metformin (Glucophage™). Interest in this situation was spurred by a well-informed, conscientious patient who had diligently read the product information insert that accompanied the medication. He remembered the caution against the use of preparations containing iodine while taking metformin and was concerned about the advisability of receiving an injection of ICG while he was on the drug.
Investigation into this problem included correspondence with the manufacturer of metformin (Bristol Meyers Squibb), and consultation with pharmacists in drug information centers and clinics. The manufacturer’s response expresses little concern about interaction between the two drugs, but stressed that no multi-centered trials had been conducted to prove significant contraindications, and therefore, they would not deny the possibility of complications in using the two preparations together. They stipulated that metformin should be discontinued at the time of administering ICG and recommended waiting at least 48 hours after ICG injections before restarting the metformin, or until renal status can be determined. In this letter we will present the rationale behind this recommendation, and demonstrate that the warnings are probably unfounded.

The argument is by analogy to iodine-containing radiocontrast dyes such as diatrizoate or iopamidol. These dyes have a low but non-negligible incidence of renal damage whose etiology is as yet poorly understood. Some of the evidence points to dye-induced renal vasoconstriction leading to ischemia. There is also substantial evidence that the dyes have direct toxic effects on the epithelial cells of the nephron. Studies are underway to determine which of these and other proposed mechanisms are the main causes of renal failure. It should be noted that radiocontrast induced nephropathy (RCIN) is rare, occurring only in patients with predisposing risk factors such as diabetes, pre-existing renal insufficiency, and congestive heart failure. The incidence in the general population is estimated as between 2–7%.

Metformin is exclusively eliminated by the kidneys; thus renal failure results in high concentrations of metformin. One of the side effects of metformin is a condition known as metformin associated lactic acidosis (MALA) in which extremely high levels of lactic acid are produced by the body for reasons which are far from clear at present. The condition is fatal in approximately 50% of the cases, so even though the overall incidence is low (0.084 cases per 1000 patient years), extreme caution is warranted when prescribing metformin. The list of risk factors for metformin is extensive. Renal failure, cardiac failure, ischemic heart disease, proteinuria, peripheral vascular disease, and pulmonary disease have all been implicated as identifiable risk factors for onset of MALA. Oddly, however, high levels of metformin appear not to be significant risk factors for MALA. Thus, although the renal failure caused by radiocontrast dyes invariably will lead to high metformin levels, it is not at all certain that lactic acidosis necessarily follows.

ICG has been incorrectly classed with the radiocontrast dyes as a contraindicated drug for patients taking metformin. The reason is that it too contains iodine, and it is relatively certain that the iodine in the radiocontrast dyes is somehow responsible for their nephrotoxicity. However, our searches of the literature indicate that this reasoning is flawed. For one thing, iodine is covalently bound to the organic components of the radiocontrast dyes, and is therefore the source of their radioopacity, while the iodine in ICG is in the form of sodium iodine added to improve its solubility. ICG is a fluorescent compound, not a radiocontrast material, and the iodine is not part of the empirical ICG formula. The link between iodine and RCIN is unclear, but it seems intuitively obvious that the covalent bonding is necessary to effect the kinds of toxicities leading to renal failure.

Secondly, many drugs contain iodine, but to our knowledge radiocontrast dyes are unique in their nephrotoxic effects. Amiodarone and iodoquinol, among others contain covalently bonded iodine, but there is no evidence for renal damage from these compounds, and the manufacturers of metformin offer no warnings on the simultaneous use of these drugs. More specifically, sodium iodide and potassium iodide are not listed as contraindicated drugs when taking metformin. Thus the possibility of metformin–radiocontrast dye toxicities are unlikely to be of concern when using ICG. There are no reported cases of ICG induced nephrotoxicity. In any case, the minimal risks of MALA must be compared to the benefits derived from ICG choroidal angiography by the attending physician.

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REFERENCES