

Skin testing and adverse reactions in fluorescein: A prospective study

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ABSTRACT

Sodium fluorescein (SF) is widely used to assess chorioretinal disorders. Adverse reactions are well documented but the underlying mechanism is still uncertain. The aim of this study was the evaluation of skin testing to predict SF reaction, the identification of possible predisposing factors, and the objective record of the reported reactions. All patients with adequate indication for SF angiography (SFA) during an 18-month period were evaluated as follows: (a) detailed personal history of atopy, diabetes, previous SFA, and/or diagnostic procedures with radiocontrast media (RCM) and possible side effect; (b) skin testing with SF 10% diluted preparations; (c) SFA with 5 mL of SF, objective record of any reaction. Two hundred twenty-four patients (108 men and 116 women) with a mean age of 65.2 years (SD, 12.86; range, 16–92 years) underwent SFA. The overall rate of adverse reactions was 3.6% (8/224), which consists of 5 (2.2%) individuals with transient mild nausea; 2 (0.9%) subjects with face and upper trunk flushing that appeared in one case after 60 minutes and in the other case 24 hours later and both resolved without treatment, and 1 subject with transient bilateral frontal headache and dizziness. None of the 224 patients had positive skin or intradermal testings. One hundred thirty-six of 224 (60.7%) patients stated no previous SFA and 74.1% had not performed RCM injection. None of the recorded variables correlated with increased risk of reaction. SFA is a safe procedure with minor adverse effects. Although in vivo testing can not identify reactors it may help to exclude an underlying IgE-mediated mechanism in susceptible individuals.

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Fluorescein, a derivative of the dye galleon, was first synthesized by the famous scientist and Nobel laureate Johann Baeyer almost 140 years ago. In 1961, Alvis and Novotny, during basic research, introduced the sodium salt of fluorescein, a low molecular weight, highly water-soluble compound with fluorescent properties.¹ During the last 40 years, sodium fluorescein angiography (SFA) has become the leading technique that revolutionized the diagnostic and therapeutic approaches of numerous chorioretinal diseases.

Increasing clinical demand of SFA has raised the interest for records of adverse effects, identification of probable predisposing factors, and, predominantly, elucidation of possible underlying mechanisms. Reactions to i.v. fluorescein are well described in the literature and include nausea and vomiting, acute urticaria angioedema, flushing, and anaphylaxis.^{2,3} Adverse reactions usually are mild in severity and last for seconds to minutes but reports of serious reactions and deaths

also exist.⁴ Recently, there have been two cases of unpublished but publicized incidences of death associated with SFA in Australia.

The exact pathogenic and immune mechanism of adverse reactions to fluorescein is still uncertain and may be multiple. Although anaphylactoid reactions are believed to be the prevalent type of reaction found with i.v. fluorescein,⁵ reports of well-documented IgE-mediated anaphylaxis with positive skin-prick tests (SPTs) also exist.⁶ Having this data in mind, as well as that the relative literature consists mainly of retrospective reviews and case report, we have conducted this study to evaluate skin testing as a tool to predict SF reaction, to identify possible predisposing factors and to record objectively the occurring reactions.

MATERIALS AND METHODS

This study was performed at Allergy Unit and the Department of Ophthalmology of Attikon University Hospital in Athens, Greece. All patients with adequate indication for SFA between January 2, 2005 and July 5, 2006 were informed from ophthalmologists for the possible side effects and the aim of the study and then were directed to visit the Allergy Unit. The following data in each individual were collected from an allergy specialist: (a) detailed personal history of atopic status⁷

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defined clinically as symptoms of allergic rhinitis (itching, sneezing, increased secretion, and blockage) with or without conjunctivitis and/or allergic asthma (wheezing and dry cough) and/or immediate food allergy reaction; eczema is not evaluated as atopic criterion because of the atypical clinical presentations that may coexist in elderly patients who were the vast majority of the participants; (b) personal history of diabetes mellitus; (c) record of previous SFA and possible adverse reactions; and (d) diagnostic procedures with radiocontrast media (RCM) performed previously and possible side effects.

Consequently, SPTs were performed with 100 mg/mL of SF (SF, 10%; Institute of Pharmacological Research and Technology, Pallini, Greece) and intradermal (ID) injections of 0.2–0.3 mL with 1/1000, 1/100, and 1/10 dilutions of the 100-mg/mL SF preparation. Positive (1% Histamine chloride solution; Stalergenes, Paris, France) and negative (50% glycerin saline solution) controls are used, respectively.

According to the procedure all patients were diluted with 2.5% phenylephrine before the administration of i.v. fluorescein solution. The reagent used was the same as the aforementioned in skin testing and the volume injected was 5 mL in most cases. The ophthalmology specialist that was present recorded any adverse reaction (time of onset, symptoms and signs—blood pressure, heart rate, and peak expiratory flow rate, which were recorded also before the SF injection); if adverse reactions occurred, an allergist was called for further medical assistance and consultation. Ethics Committee of Attikon University Hospital of Athens approved the study protocol.

RESULTS

During the study period 248 patients with adequate indication for SFA were referred to the ophthalmology department. Twenty-four of 248 (9.68%) patients refused to take part in the study. The remaining 224 patients (108 men and 116 women) with a mean age of 65.2 years (SD, 12.86; range, 16–92 years) performed the study procedure and were included in the analysis.

The overall rate of adverse reactions was 3.6% (8/224), which consisted of (a) five (2.2%) patients with nausea occurring 1–3 minutes after SF infusion and automatically resolving 10–30 minutes later without treatment, (b) two (0.9%) patients with face and upper trunk flushing that appeared in one case after 60 minutes and in the other case 24 hours later and both resolved without treatment in a 3- to 4-hour period, and (c) one (0.45%) patient with transient bilateral frontal headache and dizziness starting in the 1st minute after infusion and lasting for almost 60 minutes with gradually decreasing severity after the first 15 minutes. In four out of eight reactors (three with nausea and the

one with headache and dizziness), transient increased heart rate was detected without alterations of the other measurements. Table 1 presents full recorded data of the reactors.

Thirty-one of 224 patients (13.8%) had a positive atopic status and none of them presented adverse reaction; all reactors had a negative personal history of atopy. Besides, 107/224 (47.8%) patients were suffering from diabetes and the remaining 114 (52.2%) patients had normal serum glucose levels; consequently, five of eight (62.5%) of the patients were diabetic.

Previous FA in our study population was performed in 88/224 patients (39.3%)—52 subjects once, 18 subjects twice, 9 subjects for three times, and 9 subjects for four— and 136/224 patients (60.7%) underwent the procedure for the first time. Two subjects reported mild nausea during a previous FA (one who reacted again with identical symptoms [subject 7 in Table 1] and another woman who was 44 years old and presented only mild nausea; however, she did not reproduce any symptom in the current SFA).

Fifty-eight of 224 patients (25.9%) reported a previous diagnostic procedure with RCM injection but none of them reported any adverse effect related to the examination. No positive skin or ID test was detected in any of the 224 tested patients (0%). Statistical analysis to estimate if previous SFA or personal history of prior RCM procedure predispose to SFA adverse reaction (paired *t*-test for equality of means; SPSS 10.0, SPSS, Inc., Chicago, IL) failed to prove any positive correlation.

DISCUSSION

This study is the first prospective report of adverse reactions after FA and in a simple but well-designed way, proves the limited value of skin testing before SFA as a predictor of reaction. Keeping in mind the small sample size, it also suggests that prior use of RCM or previous SFA as well as positive history of atopy do not correlate with increased reaction rate. Finally, none of the observed reactions proved to be IgE-mediated judging from negative *in vivo* tests combined with clinical appearance.

Today, SFA represents a standard tool in the investigation and management of retinal diseases, so the number of SFAs performed worldwide increases significantly year by year; statistics referring to the United States showed that >1,000,000 SFAs were performed in 2002 and this figure did not even include those performed privately whereas 10 years earlier, ~200,000 fluorescein angiograms were performed.⁸

Adverse reactions of SF generally are classified as mild, moderate, severe, or death in ophthalmology literature depending on the duration of the effect, the necessity for medical intervention, the time required

Table 1 Full demographic data of the patients with adverse reaction to FA

Patient No.	Age (yr)	Sex	Diabetes	Atopic Status	Previous FA (No.)	Previous RCM Procedure	Previous FA Reaction	Adverse Reaction
1	57	Female	No	No	No	No	No	Nausea 1 min after infusion
2	68	Male	No	No	Yes (2)	No	No	Nausea 3 min after infusion
3	47	Female	Yes	No	No	Yes (2)	No	Flushing on face-trunk in 60 min, resolved in 180 min
4	62	Male	Yes	No	Yes (1)	Yes (1)	No	Headache, dizziness in the 1st min, resolved in 60 min
5	63	Male	No	No	Yes (4)	Yes (1)	No	Nausea 2 min after infusion
6	62	Female	Yes	No	No	No	No	Flushing on face-trunk almost 24 hr later, resolved in 3-4 hr
7	63	Male	Yes	No	Yes (3)	No	Yes (nausea)	Nausea 2 min after infusion
8	56	Male	Yes	No	No	No	No	Nausea 3 min after infusion

for its resolution, and the final outcome.⁴ One major survey was performed >20 years ago with 2434 responding ophthalmologists reporting that 221,781 fluorescein angiograms were performed in 1984 and they found that the frequency rate for a moderate reaction was 1:63, for a severe reaction was 1:1900, and for death was 1:222,000. An Australian group recently published a retrospective review of 11,898 fluorescein angiograms with 132 (1.1%) adverse reactions recorded. The commonest adverse reactions were nausea (0.7%) and vomiting (0.4%) while no serious adverse reactions or deaths were recorded.⁹ In other similar reports the incidence of mild reaction is variable, *e.g.*, the incidence of nausea ranges between 0.8¹⁰ and 15%,¹¹ and vomiting ranges between 1¹² and 4.2%.¹³ In our study the overall rate of adverse reactions was 3.6% with nausea being the prevalent symptom (2.2%). All adverse reactions were mild in severity. The relatively higher observed prevalence of adverse reactions in our study can be attributed to the prospective design that ensures the record of even minor reactions. In retrospective studies, mild and transient symptoms often are not recorded, leading to underestimation of the calculated prevalence. As already mentioned, no severe adverse reaction was recorded in our population; this finding is consistent with reports of previous studies in which severe reactions have an incidence of about 1/18,020 to 1/1900.^{4,14}

Numerous studies have been performed to identify possible factors affecting adverse reaction after SFA. First, parameters related to the procedure technique (different concentrations of fluorescein,¹⁵ normal or slow rate of injection,¹¹ volume of fluorescein injected, temperature of SF solution during SFA, and differences in formulating and manufacturing processes among used reagents) were investigated with interesting results but not definite conclusions. Moreover, one study on sex effect suggested that men reacted adversely more frequently than women to fluorescein injection without clarifying any apparent cause for the increased frequency in men.¹⁶ Our small sample does not permit to argue about this statement. However, in our study, atopic status did not correlate with reaction rate; of 13.4% atopic individuals, none reacted.

Nevertheless, one of the factors that have been investigated is previous SFA and the possible higher incidence of adverse reaction in subsequent injection. Kwiterovich *et al.*² found a different frequency of adverse reactions in patients undergoing their first SFA (5.1%) in comparison with the observed frequency among patients with reported reaction during previous SFA (48.6%) and subjects with previous SFA without any adverse effect (1.8%). On the contrary, in our study the reaction rate in patients who were not previously SFA tested (3.68%) was almost the same with that (3.41%) computed in patients who reported previous

SFAs. Our results are consistent with another study that found that 77% of the nausea reactions that occurred after the first SFA were not reproduced in subsequent SFAs.¹¹ Nevertheless, our study was the first one, to our knowledge, that investigated the possible relationship of adverse reaction to SFA with previous RCM procedures and reported reactions. Our results failed to show any trend for such correlation; three of eight patients who reported adverse reactions had undergone RCM procedures without any complications. Additional investigation and mainly increasing the sample size may help to exert definite conclusions.

The clarification of underlying pathogenic and immune mechanisms of adverse reactions to fluorescein still is obscure. Histamine release has been strongly implicated; in one series, plasma level was raised in 66% of the patients with adverse reaction while complement proteins C4, C3, C1q, B factor, and the total hemolytic complement activity were decreased in all subjects given i.v. SF.¹⁷ Mast cell activation was thought to be the cause of histamine release as serum tryptase levels were elevated significantly.¹⁸ Anaphylactoid reactions are now believed to be the main type of reaction found with i.v., oral, and even topical fluorescein.¹⁹ IgE-mediated mechanism has been confirmed in certain cases with *in vivo* testing.²⁰ Accordingly, successful fluorescein desensitization has been performed in a 66-year-old male patient who experienced edema of the face and hands and had positive SPT in fluorescein.²¹

It is generally accepted that skin and ID testing is the best diagnostic procedure for IgE-mediated drug reactions. However, concerning SF adverse reactions, some authors claim that skin testing seems useless in attempting to predict allergic reactions in susceptible patients.²² Although the performed skin and ID tests in our patients were all negative, we disagree with previous suggestions. We admit that IgE-mediated reactions to SF are rare but, indisputably, they represent the most dangerous adverse reaction, in particular in the specific population that undergoes SFA (elderly people, with concomitant medications, often suffering from diabetes and/or coronary disease). In addition, the negative predictive value of skin testing seems reliable; no irritant reactions are detected. Therefore, we believe that *in vivo* testing may be important in high-risk patients, especially with increasing clinical demand of SFA in daily practice. We must not neglect the safety issue; common practice of prophylaxis with antihistamines and corticosteroids does not refer to IgE-mediated reactions but only to those of anaphylactoid type.²³

Conclusively, adverse reactions to i.v. SF are rare, but underlying immunologic mechanisms and especially IgE-mediated anaphylaxis are in some cases well documented. Although skin testing can not predict the

commonly observed reactions, it may help in the identification of the severe reactors; extended studies are needed to have conclusive results, especially with the continuing increasing use of fluorescein angiography in the ophthalmology practice.

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