Risks and precautions in the use of dyes for angiography in ophthalmology.

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Introduction

Vital dyes are used for many years in **many** applications. **The increase in their** use in the medical field is responsible for an increase in the number of cases of anaphylaxis or hypersensitivity. Practitioners should be aware of this risk and clinical features of the adverse reactions of the dyes. In ophthalmology, fluorescein is responsible for reactions that can sometimes **cause death** (1, 2). Since 2005 and the announcement by the ANSM (French National Agency for Medicines and Health Products) (3) of an increase in cases of serious **side effects** as a result of the distribution of the fluorescein AK-Fluor in France, a warning has been made against performing fluorescein angiography due to the allergic risk and recommends limiting this type of examination **in certain** indisputable indications. The HAS (French health authority) has developed with the support of the SFO (French Society of Ophthalmology) a **backgrounder** in which this risk is explained and proposes the use of oral premedication to "prevent or limit intolerance reactions", as was the usual practice before administering iodinated contrast agents (4). Despite the current practice of premedication by ophthalmologists before performing fluorescein angiography, the mechanisms of hypersensitivity reactions to fluorescein remain poorly understood and the benefit of such a practice is not clearly demonstrated. Currently, the premedication with glucorticosteroids before **the use of** iodinated contrast agents **is recommended only in case of allergy known or suspected in these products (5). The benefit of premedication** in the context of fluorescein angiography has not been reassessed. The purpose of this document is to update knowledge of dye hypersensitivity or allergy phenomena in ophthalmology.

1. Fluorescein

This substance was discovered and synthesized by Adolf von Baeyer in 1871. **He** synthesized it from resorcinol and phthalic anhydride and called it resorcinphthalein. It is referred to as "fluorescein" since 1878. Fluorescein is composed of two phenol molecules linked to a pyran cycle itself linked to a benzoic acid. Its molecular weight is 376 daltons. This acidic substance derived from xanthene is reddish in color but has fluorescent properties. **Its emission spectrum is located in** the yellow-green spectral range (530 nm) after blue light excitation (488 nm). This property is used in many fields: industry, molecular biology, hydrobiology. In ophthalmology, it is used since the 1960s to perform retinal angiography (6).

Incidence of adverse reactions

In most studies, the adverse reactions are classified according to their severity. In general, the local cutaneous (urticaria, erythema, pruritus), digestive (nausea, vomiting) and respiratory manifestations which are transient and require no **specific** treatment (dyspnea, wheezing), are considered mild. The moderate adverse reactions require treatment but are not life-threatening (urticaria, syncope, fever, paralysis...). The reactions classified as severe require urgent treatment and are directly life-threatening. They generally include respiratory and/or hemodynamic disorders (dyspnea, bronchospasm, hypotension, loss of consciousness and cardiorespiratory arrest) (7). The lack of standardization of the assessment and classification of the various adverse reactions partly explains **the wide variation of impact** from one study to another.

In 1968, a French study has reported adverse reactions to fluorescein during angiography (8). In 1974, **Hayreh reported** 3 cases of urticaria in 2,000 patients injected. **He insisted** on the possibility of vasovagal response not necessarily related to fluorescein itself (9). In 1980, a review has reported an estimated risk of severe reactions of 0.4% (10). They included vasovagal response, bronchospasm, circulatory or respiratory arrest **and** myocardial infarction. Meanwhile, the incidence of mild reactions was estimated at about 10%, including the occurrence of nausea and vomiting. This review focused on the low risk of allergy to the molecule. Finally, one of the largest **series of follw-up** remains that by Yannuzzi, published in 1986 in which 222,000 angiography examinations were analyzed. It reported a frequency of severe hypersensitivity of 1 out of 1,900 cases and only one case of death in the 222,000 examinations performed (7).

It appears from newer studies (11-13) that the risk of severe reactions has not changed over time (0, 0.16 and 0.38%, respectively).

It is worth noting that no adverse effects have been reported during pregnancy.

Nature of hypersensitivity reactions

Some reactions have a true allergic origin, i.e. are mediated by specific IgE directed against fluorescein. IgE lead to mast cell and basophil degranulation with release of tryptase and histamine, responsible for the symptoms. An allergic reaction should be suspected in patients experiencing urticaria, exanthema, pruritus, angioedema or asthma-like bronchospasm (Table 1)(14). A few cases of "true" anaphylactic shock to fluorescein have been demonstrated in the **literature** based on positive skin tests to fluorescein (15-18). **Both cases have also benefited from a second review after effective desensibilisation** (17, 18). There are cases of anaphylaxis but they seem to be extremely rare since studies report a rate of positive skin tests before angiography of 1/1,037 (13) and 1/153(16). These tests have shown no predictive value with regard to the risk of reaction or its severity. **The phenomenon of anaphylaxis implies a prior contact with the fluorescein, the so-called phase is the allergen awareness**. It should be noted that in these studies, 2 out of 3 patients were positive to the *prick test* (specific for IgE-mediated allergy) although none of them had ever undergone angiography. This suggests that sensitization to fluorescein may take place by means other than angiography and/or IV dye injection. Sensitization could take place during fluorescein corneal staining (11).

Most immediate hypersensitivity reactions are therefore non-allergic reactions. These reactions formerly known as anaphylactoid reactions result in allergy-like symptoms (Table 1), but are often milder. Various mechanisms are involved. The most well-known is the non-specific histamine release, which is related like in anaphylaxis to mast cell and basophil degranulation. This degranulation is not mediated by IgE and may be due to the direct action of a drug or molecule (for example via membrane receptors). Non-specific histamine release is more common in atopic patients. The other mechanisms are less well-known but also explain the frequency and variability of symptoms: bradykinin accumulation, leukotriene synthesis, complement activation (14). Non-specific histamine release phenomena **is** reported for fluorescein, but its mode of action is unknown. In addition during angiography, it is sometimes difficult to distinguish frequent vagal manifestations from mild manifestations due to a non-specific histamine release.

Many retrospective studies point out that the risk of developing a reaction to fluorescein is increased in all patients with history of allergy (11, 19). A prospective study has also shown that the occurrence of mild or moderate hypersensitivity reactions was higher in diabetic and allergic patients (12) but this study used an agent containing 25% of fluorescein, whereas in France only contrast agents containing 10% of fluorescein are available. Another recent prospective study has failed to confirm these results, showing that neither atopy nor having

performed previous angiographic examinations increased the risk of reaction (13). Finally, a brief review of the literature reveals that no data shows the occurrence of events in patients with shellfish allergy (20).

Interest of premedication and precautions for use

According to HAS recommendations, premedication may be proposed to patients with history of allergy or atopy, treatment with beta blockers, asthma or hypersensitivity reactions to the contrast agent during previous examinations (4). The HAS information sheet states that premedication does not prevent the occurrence of serious reactions. There is currently no evidence of the benefit of premedication, no study has compared the occurrence of adverse reactions with and without premedication. It may be based on an oral treatment with corticosteroids, antihistamines (21) or both the day before and/or the day of the examination. Some authors advocate the use of an intravenous injection of hydrocortisone before the examination. In the Vidal, the data sheet of the fluorescein sodium solution 10% from Faure only contraindicates the use of this medicine in patients with hypersensitivity to fluorescein or to any of its excipients.

Recommendations recall that an examination must be done before looking for factor of risk of hypersensitivity (asthma, drug or shellfish allergy…) and aggravating factors in patients who experienced anaphylactic shock (administration of beta blockers). In all cases, a resuscitation equipment **must be** available and the line used should be maintained for at least 5 minutes in the event of potential reactions.

These recommendations are based on the results of previous retrospective studies (7, 11, 18). The only prospective study using fluorescein 10% failed to identify factors promoting hypersensitivity reactions, including history of allergy/atopy (13). It is interesting to note that in the UK recommendations on AMD (age-related macular degeneration), the chapter on fluorescein angiography specifies the need to obtain patient consent and history but using premedication (antihistamine) is only recommended in patients with history of mild reaction during a previous angiographic examination (22).

2. Indocyanine green (ICG)

ICG is a water-soluble dye with a molecular weight of 776 kD, (**one** of fluorescein is 376 kD), which partly explains its low diffusion. ICG high plasma protein binding (98%) enhances the visibility of choroidal vessels and explains its low exudation through the blood vessel walls, even through the pores of the choroidal vessels. The dye is rapidly eliminated via hepatic excretion with an initial rate of excretion of 18-25%, resulting in a plasma half-life of 2-3 minutes with limited detectable recirculation. The ICG molecule itself does not contain iodine,

but some steps of the manufacturing processes use iodine whose residues may persist in the final product. A French laboratory (Serb) has developed a special synthesis process for the manufacturing of an iodine-free dye called infracyanine green which offers an excellent image quality without risk of anaphylaxis. Infracyanine is the main molecule used in France for ICG angiography.

Adverse reactions

ICG is known as causing no adverse reactions. Few studies report serious reactions following ICG angiography (23-26). However in 1994 in a series of 1,226 patients (1,923 examinations), Hope-Ross et al. have reported 0.15% of mild reactions, 0.2% of moderate reactions and only 1 (0.05%) severe reaction (25). Another study has reported 0.34% of reactions in 3,774 ICG examinations performed, including 2 cases of hypotensive shock (24). No fatal reaction has been described and these studies have not investigated the allergic/non-allergic nature of the reactions.

3. Analogy with iodinated contrast agents

An analogy can be drawn between hypersensitivity reactions to iodinated contrast agents and those to fluorescein or ICG. In 1998, the French Society of **Anaesthesiology** and Resuscitation (SFAR) has indicated in an update that the evidence of efficacy of premedication was insufficient but that it was legitimate to propose it in high-risk patients. In this review, the term "high-risk patients" **include** patients with history of anaphylactoid reaction to iodinated contrast agents but also patients with atopy or heart failure. Since 2009 (27), the French Radiology Society (SFR) no longer recommends the use of premedication. It opposes non-allergic hypersensitivity reactions due to a non-specific histamine release to allergic hypersensitivity.

In patients experiencing a reaction to the contrast agent, it recommends investigating the type of reaction by measuring the histamine and tryptase plasma levels (increased in patients with allergy (28)) and performing skin tests 6 weeks to 6 months after the reaction. In patients with specific allergy to the contrast agent, no prevention may be effective and the contrast agent should not be **used again**. Note that the data sheet specifies that asthma and atopy may increase the risk of non-allergic hypersensitivity and that H1-antihistamines could reduce mild or moderate symptoms of reactions (grade 1 and 2 of the Ring and Messmer classification (29)). The beneficial effects of such a premedication are not established regarding serious reactions (grade 3 and 4 of the Ring and Messmer classification (29)) (Table 1). This data sheet **reflects the conclusions** of a comprehensive review on the **literature** published in 2009 in the Journal *La Revue de Médecine Interne* (30) that clearly

concludes that premedication is not beneficial to reduce the risk of allergic reaction to iodinated contrast agents.

This approach has been partially included in the HAS transparency commission reassessment of iodinated contrast agents in May 2013 (5) where premedication with corticosteroids is only proposed in patients with known or suspected allergy, without certainty about its efficacy.

Conclusion

Immediate hypersensitivity reactions are described during or following fluorescein and, to a lesser extent, indocyanine green angiography examinations. These hypersensitivity reactions may sometimes be severe. Most reactions are mild. They are also mostly related to non-allergic hypersensitivity. True allergy cases exist. In patients with any suspicious allergic reaction, i.e.

- urticaria,
- exanthema,
- pruritus,
- angiedema,
- bronchospasm

a blood test with histamine and tryptase assay should be performed in emergency. An allergic assessment with skin tests should also be planned to incriminate the relevant dye. There is insufficient evidence in the literature regarding the efficacy of premedication to decrease the risk of serious reactions. Its use should not be systematic but possibly proposed to atopic patients who have a higher risk of non-specific histamine release. In this case, it is indicates to administer only H1-antihistamines 2 hours before the examination. Conversely, in the absence of evidence of efficacy, it should not be used in patients with history of reactions experienced during a previous examination without prior allergy assessment.

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