

Hypersensitivity to Contrast Media and Dyes



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KEYWORDS

• Hypersensitivity • Radiocontrast media • Gadolinium-based contrast media • Dyes • Fluorescein • Blue dyes • Diagnostic procedure • Management

KEY POINTS

- Increasing use leads to an increased incidence of hypersensitivity reactions to diagnostic contrast media and dyes.
- Immediate clinical manifestations are those of anaphylaxis and urticaria/angioedema, although with radiocontrast media nonimmediate exanthems also may occur.
- Skin tests (and possibly laboratory tests) are helpful for the confirmation of allergy and the exclusion of skin-test-positive alternative preparations for future procedures in those patients with positive test results.
- In all other patients, consideration of the necessity, premedication, selection of a preparation as structurally different as possible, and preparedness for emergency is recommended.

HYPERSENSITIVITY REACTIONS TO IODINATED RADIOCONTRAST MEDIA

Iodinated radiocontrast media (RCM) are concentrated solutions of tri-iodinated benzene derivatives used for diagnosis and treatment of vascular disease by enhancement of radiographic contrast. Although the risk of an adverse reaction after a single RCM administration is low, RCM are among the most common elicitors of anaphylaxis and exanthemas, owing to the administration of more than 75 million procedures per year worldwide.¹ Reactions may be classified into immediate (<1 hour) or nonimmediate (>1 hour after administration) hypersensitivity reactions, or toxic reactions related to the well-known toxicity of the compounds (eg, nephrotoxicity, neurotoxicity), or may also be caused by factors totally unrelated to RCM, such as chronic idiopathic urticaria (**Fig. 1**).² Four structurally different RCM (monomeric and dimeric, ionic and

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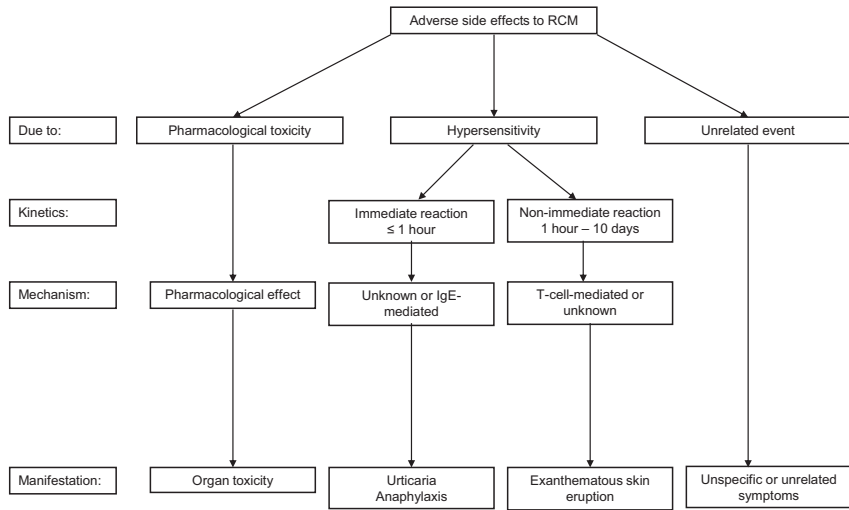


Fig. 1. Classification of adverse reactions to radiocontrast media (RCM). IgE, immunoglobulin E. (Adapted from Brockow K, Christiansen C, Kanny G, et al. Management of hypersensitivity reactions to iodinated contrast media. *Allergy* 2005;60:157; with permission.)

nonionic) are on the market, with nonionic monomers as the most commonly sold products, whereas ionic monomers for intravenous use have been withdrawn in most countries.

Incidence and Risk Factors

Immediate hypersensitivity reactions (IHRs) have been reported in 0.7% to 3% of patients receiving nonionic RCM, severe reactions in 0.02% to 0.04% of intravenous procedures, and fatal IHRs in 0.00001% to 0.0003% of contrast media applications.³ Exanthematic nonimmediate hypersensitivity reactions (NIHR) affect 0.5% to 3% of RCM-exposed patients; higher frequencies have been reported, but seem to be less reliable.^{1,4} There is a higher incidence of nonimmediate exanthemas associated with dimeric nonionic RCM.⁵

The main risk factor for IHR and NIHR is previous severe reactions.⁶ Further less prominent predisposing factors reported were female gender, renal insufficiency, a history of doctor-diagnosed asthma, drug allergy, food allergy, contact allergy (for NIHRs), and interleukin-2 treatment (for NIHRs).^{6–9} Repeated exposures to RCM increase the risk of IHRs.¹⁰ An immediate reaction is not a risk factor for developing NIHR, and vice versa.¹

Clinical Manifestations

The onset of IHR is rapid. About 70% occur within 5 minutes after injection, and 96% of severe reactions manifest within 20 minutes.^{11,12} Pruritus and urticaria/angioedema occur in about 70% of patients with IHR.^{3,13} Heat sensation, nausea, and vomiting may occur but also may be rather toxic reactions when not accompanied by other symptoms, such as abdominal pain and diarrhea. Severe reactions of the respiratory and cardiovascular systems are dyspnea, bronchospasm or tachycardia, and hypotension, sometimes with loss of consciousness.¹ Fatal reactions may occur.

Maculopapular exanthems occurring hours to several days after the RCM administration are typical NIHRs.¹ Other, less frequent manifestations of nonimmediate skin

reactions include fixed drug eruption, erythema exsudativum multiforme, pompholyx, symmetric drug-related intertriginous and flexural exanthema, or drug-related eosinophilia with systemic symptoms (DRESS).¹ Nonimmediate RCM reactions typically are mild or moderate in severity. Exceptional, life-threatening, or fatal cases are associated with vasculitis, Stevens-Johnson syndrome, toxic epidermal necrolysis, or delayed anaphylactic reactions.^{1,14}

Pathophysiology

For IHRs, an immunoglobulin E (IgE)-mediated allergic mechanism can be demonstrated only in a minority of cases. However, an alternative mechanism, such as a direct membrane effect possibly related to the osmolality of the solution, an activation of the complement system, or direct bradykinin formation, has also never been convincingly shown to be present in vivo selectively in reactors.¹⁵ IHRs are associated with histamine release from basophils and mast cells.¹⁶ There are reports of high levels of tryptase in connection with severe or fatal reactions.^{16,17} Positive immediate skin tests, the detection of contrast media-specific IgE in patients with IHRs, and positive basophil activation tests in a subgroup of patients support the principal concept of an IgE-mediated mechanism.^{9,15,18}

NIHRs induced by RCM are T-cell mediated. Reported onset of skin eruptions 2 to 10 days after the first exposure, immunohistologic studies of exanthemas and positive skin-test sites showing a perivascular infiltrate of CD4⁺ and CD8⁺ T cells with expression of CD25, HLA-DR, CLA, and CD69, and positive delayed skin tests argue for a type IV allergic mechanism.¹⁵ In addition, peripheral blood mononuclear cells from patients showed in vitro proliferation in the presence of the culprit RCM when added to the culture, and expressed an increase in different lymphocyte activation markers (eg, CD69, CD25, HLA-DR, CLA).^{19,20} RCM-specific T-cell clones have been generated.¹⁹

It is interesting that no previous sensitization phase seems to be necessary in IHR and NIHR.¹⁵ NIHR may occur after first contact with a single dose of RCM after 5 to 10 days.²¹ Allergy to iodine does not play a major role in RCM hypersensitivity, as only exceptional patients reacted to a provocation test with Lugol solution.²²

Diagnostic Methods

In IHRs, elevated histamine or tryptase in plasma and serum, respectively, in comparison with baseline, may confirm anaphylaxis to RCM.²³ Blood samples should be obtained as soon as possible for histamine and 1 to 2 hours after the onset of symptoms for tryptase. Further allergologic workup is recommended between 1 and 6 months after the reaction (**Table 1**).²³ Skin-prick test (SPT) with undiluted RCM is performed before intradermal tests (IDTs) with substances diluted 10-fold in sterile saline. Readings are done after 15 to 20 minutes. For NIHRs and unclear reactions, delayed readings of IDTs and patch tests are also done after 48 and 72 hours, and optionally at other time points such as at 24 or 96 hours in cases of local pruritus or erythematous plaques. Patch tests should be performed with undiluted substances. Because cross-reactivity is frequent, it is advised to test a panel of several different RCM in an attempt to find a skin-test-negative product for future RCM examinations.²³ In vitro tests, such as the basophil activation test, the lymphocyte transformation test, and the lymphocyte activation test, appear to be of value, as they are positive in previous reactors^{14,24}; however, their sensitivity and specificity has not yet been firmly established. Provocation tests with progressive increases of the injected RCM dose over several days are useful to confirm a negative skin-test result in NIHRs.^{25,26} This procedure has also been reported in IHRs without severe reactions by one European study group.²⁷ Because of the potential risk involved, provocation tests should be

Table 1 Skin-test concentrations recommended for iodinated radiocontrast media and gadolinium-based magnetic resonance contrast media			
Test	Concentration ^a	Readings	
		Immediate Reaction	Nonimmediate Reaction ^b
Skin-prick test	Undiluted	20 min	20 min, 48 h, 72 h ^c
Intradermal test	1:10 diluted ^d	20 min	20 min, 48 h, 72 h ^c
Patch test	Undiluted		20 min, 48 h, 72 h ^c

^a Undiluted radiocontrast media (with an iodine concentration of 300–320 mg/mL) or gadolinium-based magnet resonance contrast media.

^b Only for radiocontrast media.

^c The reading times are tentative: if the patient notices a positive reaction (pruritus, erythema) at the skin-test site at other time points, additional readings may be performed (eg, after 24 h or 96 h).

^d For nonsevere nonimmediate radiocontrast media reactions, undiluted preparations may also be used.

Adapted from Brockow K. Immediate and delayed reactions to radiocontrast media: is there an allergic mechanism? Immunol Allergy Clin North Am 2009;29:453–68; with permission.

performed only in centers with experience in performing and monitoring these tests, and in immediate emergency treatment.²⁸

Management

Radiologists should be trained in how to treat IHRs, and an observation period of 20 to 30 minutes after the administration of the RCM has been recommended.²⁹ It has been reported that many residents were not able to administer emergency treatment appropriately.^{30,31}

Because of their very limited sensitivity and their specificity of approximately 95%, skin tests should not be used as a prescreening tool in patients without any previous reaction.³² If a patient with a past hypersensitivity reaction needs a new contrasted examination, the culprit substance should not be administered without any allergy test.²³ In such patients, skin tests are recommended. In a patient with a positive reaction to the culprit substance, a panel of RCM should be tested to find a skin-test-negative product. In most cases with IHRs and in a proportion of patients with NIHRs, skin tests will remain negative and the proper mechanism will not be identified. In these cases, a structurally unrelated RCM should be considered for the next examination. In NIHR, a graded drug-provocation test with progressive increases of the RCM dose can confirm negative skin-test responses.^{26,27} The prophylactic use of premedication in patients with previous IHRs and NIHRs is becoming more controversial, but is still commonly applied and recommended by certain investigators.³³ A combination of corticosteroids (eg, prednisolone) and antihistamines given before application are the most frequently used agents, if the culprit drug cannot be identified by skin tests. However, radiologists have to accept that severe breakthrough reactions are still possible in patients receiving premedication, if the same or a cross-reactive RCM has been used. Thus, physicians should not rely on the efficacy of premedication alone.

HYPERSENSITIVITY REACTIONS TO GADOLINIUM CONTRAST MEDIA

Gadolinium-based contrast media are paramagnetic macrocyclic or linear gadolinium-containing chelates used to highlight contrast for magnetic resonance

imaging (MRI). In subjects with renal disease, they have been associated with a disease resembling scleromyxedema or scleroderma called nephrogenic systemic fibrosis. These non-allergy-like reactions are not further discussed in this article. IHRs to gadolinium-containing intravenous contrast media have been reported, but are less frequent in comparison with those after administration of RCM.

Incidence and Risk Factors

IHRs to gadolinium contrast media have been reported in approximately 0.07% of adults and 0.04% in children.^{34,35} Of these, 74% were graded as mild, 19% as moderate, and 7% as severe.³⁴ There has been a report that abdominal MRI examinations would more frequently elicit IHRs (0.01%) in comparison with brain (0.005%) or spine examinations (0.003%).³⁶ Reported risk factors are similar to those of RCM and include previous reaction (30%), female gender, and concomitant allergies and asthma.³⁵ Controversy exists as to whether reaction rates depend on the structure of gadolinium-based substances, with higher reaction rates for gadoteridol and gadobenate dimeglumine, or if the evidence for this conclusion is as yet insufficient.^{35–38}

Clinical Manifestations

The clinical manifestations of IHRs to gadolinium contrast media do not differ from those to iodinated RCM. The most common symptoms are urticaria (50%–90%) and nausea, whereas anaphylaxis is more seldom seen.^{35,39} There is no report for NIHR.

Pathogenesis

As is the case for iodinated RCM, the mechanisms involved in IHRs to gadolinium contrast media have not been fully elucidated. However, specific positive skin tests in some of the examined patients point to a possible IgE-mediated mechanism.

Diagnostic Methods

Confirmation of an anaphylaxis by the history, the clinical picture, an increased level of tryptase or histamine during the acute episode, and skin tests using SPT with undiluted media in addition to IDT with 1:10-diluted gadolinium substances have been recommended.^{40,41} It has been reported that IDTs with undiluted gadolinium preparations were irritative and unspecific.⁴⁰ The percentage of patients with positive skin tests remains unknown; however, if positive responses do appear they have been used to guide the selection of alternative gadolinium preparations to be used in the future.⁴²

Management

In parallel with the management of iodinated RCM hypersensitivity, in patients with previous reactions to gadolinium preparations either the avoidance of gadolinium preparations and use of an iodinated RCM, or a combination of administration of a structurally different gadolinium preparation and skin testing to find a skin-test-negative product in those patients with positive skin test to the culprit, is recommended.⁴² The value of premedication in patients without a positive skin test is unknown.⁴⁰

HYPERSENSITIVITY REACTIONS TO DYES

Various natural and synthetic dyes are commonly used for diagnostic purposes in different medical conditions, especially in oncology, ophthalmology, and urology. Although hypersensitivity reactions to dyes are relatively uncommon, they can be

severe and life-threatening. Moreover, owing to the increased frequency of dye use, more patients are at risk for these adverse reactions, therefore clinicians should be aware of them. This section discusses the most widely used dyes, including fluorescein, the so-called blue dyes (Patent blue V [PBV], Isosulfan blue [IB], Methylene blue [MB]), Indocyanine green (IG), and Indigo Carmine (IC).

Fluorescein

Sodium fluorescein is a low molecular weight, highly water-soluble compound with fluorescent properties used for the study of chorioretinal diseases (Fig. 2). It allows sequential visualization of blood flow simultaneously through retinal, choroidal, and iris tissues. It has also been used in neurosurgery to identify the excision range of a brain tumor.⁴³

Incidence and risk factors

The general incidence of adverse reactions to intravenous fluorescein has been estimated as 5%, with 0.05% being severe reactions.⁴⁴ However, other investigators have reported variable rates ranging between 3% and 20%.^{45,46} In patients who underwent fluorescein angiography for the first time, Lira and colleagues⁴⁷ reported urticaria in 1.06%, bronchospasm in 0.38%, and laryngeal edema in 0.1%. Urticaria occurs in 0.5% to 1.2%^{44,48,49} and respiratory distress in 0.02% to 0.1% of patients.^{48,50} Reactions to orally administered fluorescein are observed in 1% to 2%.^{51,52}

Risk factors for IHRs to fluorescein are previous reactions to colloidal plasma substitutes,^{44,53} a history of dye allergy, diabetes, systemic arterial hypertension,^{44,54} and a history of allergy.⁴⁷

Clinical manifestations

Mild reactions (nausea, vomiting, pruritus, sneezing, vasovagal disorders, inadvertent arterial injection) are observed in 2% to 10%, moderate reactions (urticaria, other skin eruptions, syncope, thrombophlebitis, pyrexia, local tissue necrosis, muscular paralysis) in 1.5%,⁴⁷ and severe reactions in 0.05% of patients. Cardiovascular shock, myocardial infarction, laryngeal edema, bronchospasm, and tonic-clonic seizures are regarded as severe reactions.⁴⁴ Death occurred in 1 of every 200,000 patients.^{55,56} One case of a patient with bullous pemphigoid induced by fluorescein has been published.⁵⁷

Pathogenesis

The mechanisms involved in IHRs to fluorescein have not been fully elucidated. The following have been proposed⁴⁸: (1) nonallergic histamine release; (2) IgE-mediated immediate hypersensitivity^{48,49}; (3) complement activation; (4) disturbances of arachidonic acid metabolism; (5) vasovagal phenomena; (6) anxiety-related medullary sympathetic discharge; (7) direct vasospastic toxic effect; (8) contamination during the

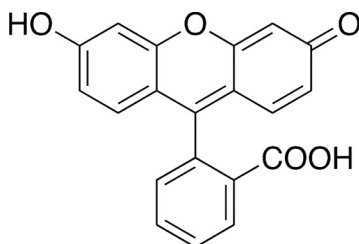


Fig. 2. Chemical structure of fluorescein.

manufacturing process; (9) destruction of the vascular endothelium through Factor XII and the coagulation system^{49,58}; (10) combinations of the above.

Diagnostic methods

Elevated serum levels of tryptase and histamine during the reaction confirm the diagnosis of anaphylaxis.^{49,59} Because the pathogenesis of IHR to fluorescein has not been clarified, there is no clear consensus among investigators regarding how to confirm hypersensitivity to this dye. The following have been used:

1. Skin tests: prick test with fluorescein 20% and IDT at 2%.⁶⁰ López-Sáez and colleagues⁶¹ used IDTs at 1:1000, 1:100, and 1:10 dilutions. Some investigators have suggested that skin tests have high sensitivity and negative predictive value,⁶⁰ but there are not enough cases from which to draw any firm conclusions.
2. Intravenous provocation test.⁶⁰
3. Conjunctival provocation. Trindade-Porto and colleagues⁶² suggested that whenever skin tests are negative, a conjunctival provocation test should be performed.

Management

Various approaches for the management of high-risk patients with fluorescein hypersensitivity have been used, including pharmaceutical prophylaxis with antihistamines⁶⁰ or a combination of antihistamines and corticosteroids, fluorescein desensitization,^{63,64} switch to oral fluorescein angiography, and the use of other alternative techniques such as optical coherence tomography. Some investigators consider that antihistamine prophylaxis has low efficacy,⁶⁰ and antihistamines and corticosteroids are not always effective.^{56,65}

Ellis and colleagues⁶⁵ proposed that antihistamines might have a place in prophylaxis against side reactions to intravenous fluorescein in patients with a history of allergies, allergic reactions to drugs, or previous reactions to fluorescein.

Patent Blue V

PBV and IB belong to the group of triarylmethane synthetic dyes (Fig. 3). These dyes basically share the same sodium or calcium salt of diethylammonium hydroxide inner salt, differ in the position of the substituted sulfonate, and are selectively absorbed into the lymphatics, bound to albumin, and excreted into the urine and bile. Both are used for demonstrating sequential lymphatic dissemination of melanoma into sentinel nodes, identification of sentinel nodes in breast cancer, to identify lymphatics for lymphovenular anastomosis, in fistulography, and for determination of cardiac output. PBV and IB are also used as food additives, in the manufacture of textiles, cosmetics, plastics, and paper, and in agriculture.⁶⁶ PBV is also known as Acid blue 3, Disulfine blue, and food additive E131.⁶⁷

Incidence and risk factors

The incidence of IHRs to PBV is reported at 0.88%, with grade I reactions (minor) at 0.48%, grade II (moderate) at 0.32%, and grade III (severe) at 0.08%,^{68,69} although higher incidence rates of anaphylaxis have been reported.^{70–73}

Risk factors for IHRs to PBV are exposure to triphenylmethane dyes from textiles, cosmetics, print shops, farms, pharmaceutical plants, food-processing plants, and plaque-disclosing agents in dentistry.

Clinical manifestations

Symptoms usually are observed after 5 to 45 minutes of PBV injection.⁷⁴ Cutaneous manifestations include large blue/green hives coalescing to form huge welts, the so-called blue urticaria, that has been regarded as pathognomonic of a reaction to

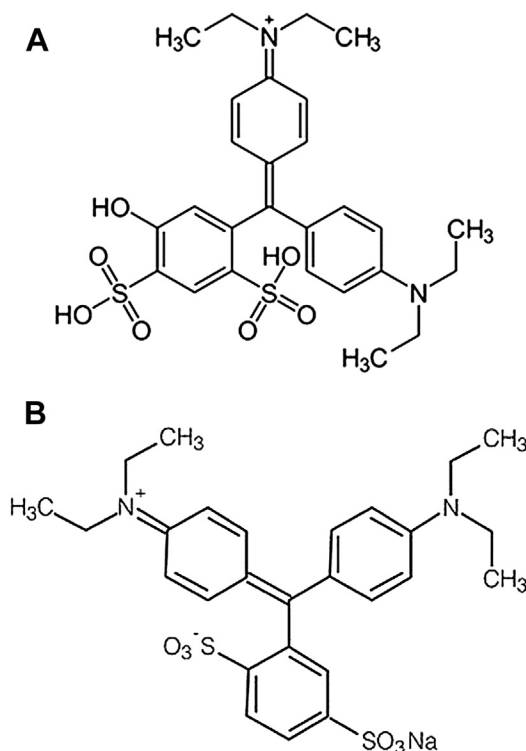


Fig. 3. Chemical structure of triarylmethane dyes. (A) Patent blue V. (B) Isosulfan blue.

PBV; blue-colored periorbital angioedema, urticaria, pruritus, erythema, and angioedema of arms and hands. Other symptoms include shock, bronchospasm, nasal congestion, and gastrointestinal symptoms. Biphasic reactions can occur,^{70,75,76} and a poor response to ephedrine and intravenous fluids and the need for adrenaline because of sustained release of the dye through lymph nodes have been reported.⁷⁴

Pathogenesis

Although reactions to PBV could be due to direct mast-cell or basophil activation, evidence for IgE-mediated reactions to PBV has been obtained from the following observations: (1) positive SPTs with PBV⁷⁴; (2) passive transfer of the sensitivity⁷⁷; (3) positive CD-sens test indicating high basophil allergen threshold sensitivity⁷⁸; (4) detection of specific IgE to PBV by enzyme-linked immunosorbent assay.⁷⁹ It is postulated that PBV may be the hapten cross-linking specific IgE antibodies after binding to a carrier.

Diagnostic methods

Increased serum levels of tryptase and histamine during reactions to PBV suggest mast cell/basophil activation and confirm the diagnosis of anaphylaxis.^{74,80} SPTs with undiluted PBV and IDTs with 1:1000 to 1:10 dilutions are recommended.^{74,80,81} Measurement of specific IgE in the serum⁷⁹ and basophil activation test⁸² can be helpful, although those are available only in a few centers.

Owing to the strong structural homology between PBV and IB, there is strong cross-reactivity among both dyes. Because MB is structurally not related to these dyes no cross-reactions are expected (see Fig. 3), but have been described.⁸⁰

Management

Various approaches have been proposed to prevent reactions to PBV, including the reduction of the amount of dye to be administered⁸³; the use of MB as alternative dye after a skin test; lymphatic mapping with radiocolloid (technetium-labeled nanocolloidal albumin); and preoperative prophylaxis with chlorpheniramine, hydrocortisone, and famotidine.^{84,85} However, although pharmacologic prophylaxis seems to attenuate the severity, it does not reduce the overall incidence of IHRs to blue dyes.

Isosulfan Blue

IB is the sodium salt of PBV, also called Sulfan blue, Food blue 3, Patent blue VF, Patent blue violet, and acid blue 1 (see [Fig. 3](#)). This dye is used for lymphatic mapping in the context of sentinel lymph node biopsy in patients with melanoma, breast, bladder, cervical, and endometrial cancer, and as a coloring agent in textiles, cosmetics, detergents, paints, inks, antifreeze, cold remedies, laxatives, and suppositories.

Incidence and risk factors

Hypersensitivity reactions to IB are observed in 0.9% to 1.9% of cases.^{66,74,76,86–88} Severe reactions are observed in 0.5% to 1.1%,^{66,76} and anaphylaxis in 0.2% to 1.1%.⁸⁹ Allergy to sulfonamides does not constitute a risk factor for reactions to IB.⁶⁶

Clinical manifestations

Symptoms start 15 to 49 minutes after exposure⁶⁶ and include anaphylactic shock requiring vasopressor support,^{70,90} blue urticaria, facial angioedema, pruritus, generalized macular rash, hypoxemia, and wheezing. Biphasic reactions may occur.^{70,75,76,91}

Pathogenesis

Sensitization occurs through exposure to a cross-reacting antigen contained in everyday products. There is evidence suggesting that reactions to IB are mediated by specific IgE⁶⁹ whereby IB would act as a hapten that weakly binds to serum proteins, but there is the possibility that some reactions are antibody-independent with direct mast cell and basophil membrane activation, or activation of the alternative complement pathway. As previously mentioned, IB and PBV show extensive cross-reactivity.

Diagnostic methods

Increased serum levels of tryptase and histamine are present in acute reactions to IB.^{92–94} SPT and IDT with IB dilutions of 1:10,000 to 1:100 confirm sensitivity to the dye.

Management

The approach for managing patients hypersensitive to IB is similar to that used in patients with reactions to PBV and include the use of smaller volumes of the dye,⁸³ the utilization of MB as an alternative for sentinel lymph node localization,^{80,95,96} and preoperative medication with antihistamines, and corticosteroids to reduce the severity of anaphylactic reactions, although this pretreatment would not prevent the occurrence of the reaction.⁹⁵

Methylene Blue

MB is a polyaromatic cationic dye of the phenothiazine group, also known as CAS No. 61-73-4, anhydrous methylene blue, CAS No. 7220-79-3, or MB trihydrate. Its structure is unrelated to the triarylmethane dyes (PBV and IB) ([Fig. 4](#)). MB is a tracer that has been used for detecting urinary tract and digestive fistulas, assessment of tubal

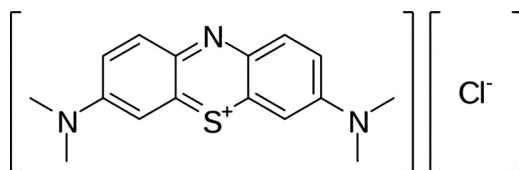


Fig. 4. Chemical structure of Methylene blue.

permeability or sentinel lymph node biopsies, the treatment of hypotension during septic shock, and for treating anaphylaxis. In lower doses it is used for the treatment of methemoglobinemia.

Treatment of fresh frozen plasma with MB is used for pathogen inactivation, a photodynamic process preventing viral RNA and DNA replication.

Incidence and risk factors

MB rarely induces hypersensitivity, and is generally regarded as a safer alternative to triarylmethane dyes for satellite node mapping.⁸⁹ MB does not cross-react with PBV and IB, although concomitant sensitizations have been described.⁸⁰

Clinical manifestations

MB rarely induces anaphylaxis, but occasionally peripheral arterial desaturation, facial angioedema, generalized urticaria, hypotension, and tachycardia have been reported.^{97–99} On the other hand, skin necrosis and ulceration have been associated with MB injection.^{100–103} Other adverse effects induced by MB include burning pain, blue macules, bluish skin discoloration, fetal congenital anomalies,^{104–106} spinal cord necrosis,¹⁰⁷ pulmonary edema,¹⁰⁸ and acute generalized exanthematous pustulosis.¹⁰⁹

MB-treated fresh frozen plasma has also been reported to induce severe allergic reactions,¹¹⁰ although this observation has not been confirmed by other investigators.¹¹¹

Pathogenesis

Anaphylaxis to MB is mediated by IgE, accompanied in 75% of cases by an increase in serum tryptase, and in 66% by an increase in histamine. Acute generalized exanthematous pustulosis is mediated by drug-specific T cells.

MB intercalates into viral nucleic acid, and subsequent illumination generates singlet oxygen radicals, leading to guanosine oxidation and destruction of the viral nucleic acid. The combination of MB and illumination alters plasma proteins, resulting in the production of neoantigens.¹¹²

Diagnostic methods

Skin IDTs with MB 1% diluted from 10^{-4} to 10^{-2} have been proposed for the confirmation of MB allergic hypersensitivity.⁸⁰ **Table 2** summarizes the concentrations of dyes for skin testing in patients with suspected allergy. The basophil activation test is an alternative investigational diagnostic method.^{99,110}

Management

MB does not cross-react with PBV and IB,^{70,97,113} and therefore constitutes an alternative dye, especially for satellite lymph node localization in patients who have reacted to triarylmethane dyes.

Table 2
Skin-test concentrations for dyes commonly used for medical purposes

Dye	Skin-Prick Tests	Intradermal Tests	Patch Tests
Fluorescein	Undiluted	1:10	Undiluted
Patent blue V	Undiluted	1:10	—
Isosulfan blue	1:1000 to 1:100	1:1000 to 1:100	—
Methylene blue	Undiluted	1:10,000 to 1:100	—

Indocyanine Green

IG is a tricarbocyanine organic dye with less than 5% iodine (see [Fig. 4](#); [Fig. 5](#)). This dye has been used for the diagnosis of conditions affecting the choroidal vasculature, and the study of cardiac output and hepatic function.

Incidence and risk factors

IHRs to IG are rarely observed. In one study, severe reactions were present in 0.05% to 0.07%,^{114,115} moderate reactions in 0.2%, and mild reactions in 0.15%.¹¹⁴ One death during cardiac catheterization with IG has been published.¹¹⁶

Su and colleagues¹¹⁷ studied the incidence of IHR to the simultaneous intravenous injection of fluorescein and IG for fundus angiography. IHRs were observed in 28 of 396 patients with drug allergy (7.2%) and in 145 of 3426 without allergy history (4.2%) ($P = .008$), while patients with an allergy history also showed more severe reactions.

Clinical manifestations

Nausea, light-headedness, disorientation, irregular pulse, shallow respiration, diaphoresis, cyanosis, hypotension, incontinence, pruritus, and wheezing are the most frequent symptoms of IHRs to IG,¹¹⁸ whereas full-blown anaphylactic shock occurs less frequently.^{118,119}

Pathogenesis

Mechanisms of IHRs to IG are unknown, and it has been hypothesized that anaphylaxis may be related to the iodine additive or the dye itself.

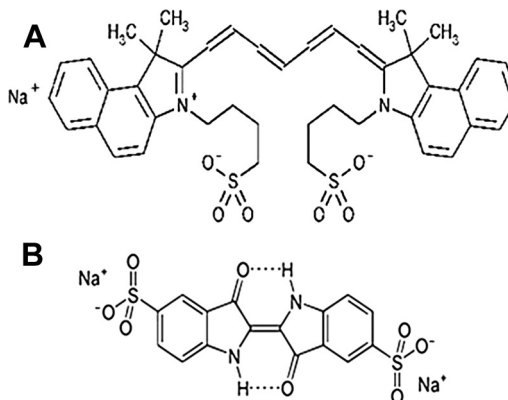


Fig. 5. Chemical structure of Indigo derivatives. (A) Indocyanine green. (B) Indigo carmine.

Diagnostic methods

No diagnostic methods have been described in the literature.

Management

In patients who have experienced an IHR to IG, avoidance of the dye is recommended.

Indigo Carmine

Indigo is produced by fermenting the *Indigofera tinctoria* plant, and has been used as a dye in denims, blue jeans, and other fabrics. Indigotine and IC are indigo derivatives widely used as synthetic coloring agents in the food and cosmetic industries (see Figs. 4 and 5).

Indigotine (FD&C blue dye No. 2) has been associated with respiratory occupational symptoms (cough, dyspnea, wheezing, and nasal congestion) and occupational asthma that was confirmed by means of bronchial provocation. IC (sodium indigotin disulfonate) is considered biologically inert and extremely safe, and it used medically for the evaluation of the lower urinary tract during cystoscopy.

Incidence and risk factors

IHRs to IC are very uncommon.¹²⁰ Allergy to sulfonamides has been suggested as a risk factor for IHRs to IC.¹²¹

Clinical manifestations

IC can rarely trigger severe life-threatening anaphylaxis and cardiac arrest.¹²² Other clinical manifestations include urticaria, bradycardia, bronchospasm, and hypotension.^{121,123}

Pathogenesis

The pathogenesis of IHRs to IC is currently unknown.

Diagnostic methods

No diagnostic methods have been described thus far.

Management

Avoidance of IC is recommended in patients who have had an IHR to the dye.

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