

PERIOPERATIVE ALLERGY: UNCOMMON AGENTS

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Anesthesia may often be considered as a high-risk procedure and anaphylaxis remains a major cause of concern for anesthetists who routinely administer many potentially allergenic agents. Neuromuscular blocking agents, latex and antibiotics are the substances involved in most of the reported reactions. Besides these three agents, a wide variety of substances may cause an anaphylactic reaction during anesthesia. Basically all the administered drugs or substances may be potential causes of anaphylaxis. Among them, those reported the most in literature include hypnotics, opioids, local anesthetics, colloids, dye, Non-Steroidal Anti-Inflammatory Drugs (NSAIDs), Iodinated Contrast Media (ICM), antiseptics, aprotinin, ethylene oxide and formaldehyde, and protamine and heparins. No premedication can effectively prevent an allergic reaction and a systematic preoperative screening is not justified for all patients; nevertheless, an allergy specialist should evaluate those patients with a history of anesthesia-related allergy. Patients must be fully informed of investigation results, and advised to provide a detailed report prior to future anesthesia.

Anesthesia is commonly regarded as a high-risk activity. Nevertheless, many Authors acknowledge that impressive safety improvements have been made in this field, so that recent reports have been able to conclude that anesthesia-related mortality has drastically decreased in the last two decades (1). However, anaphylaxis remains a major cause of concern for anesthetists who routinely administer many potentially allergenic agents. Therefore, they are considered as the medical practitioners who are most likely to see severe anaphylactic reactions.

In fact, every drug used in anesthesia has been reported to cause a reaction, and no pre-medication has proven to be able to prevent anaphylactic reactions (2). On the contrary, preventing second reactions in patients with a history of anaphylaxis, or major undiagnosed or undocumented adverse events during anesthesia may reduce the incidence of anesthetic anaphylaxis. Therefore,

a specialist in allergy-immunology should evaluate patients who have experienced anaphylaxis, in order to reduce second reactions.

CAUSAL AGENTS

The overall distribution of the various causal agents incriminated in anaphylaxis during anesthesia is similar in most reported series. Neuromuscular blocking agents (NMBAs) represent the most frequently involved substances, involved in 50 to 70% of reactions occurring during anesthesia, followed by latex (12 to 16.7%) and antibiotics (15%) (see Chapter "Epidemiology" – Table 1).

Hypnotics

Hypnotics commonly used in anesthesia are

Key words: Hypnotics; Opioids; Local anesthetics; Colloids; Dye; Non-Steroidal Anti-Inflammatory Drugs (NSAIDs); Iodinated Contrast Media (ICM); Antiseptics; Aprotinin; Ethylene oxide; Formaldehyde; Protamine; Heparins.

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0394-6320 (2011)

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thiopental, propofol, midazolam, etomidate, ketamine and inhaled anesthetics. Allergic reactions involving these modern drugs appear to be relatively rare. The estimated incidence of hypersensitivity reactions with thiopental is estimated to be 1:30 000 (3). It has been suggested that most of the generalized reactions are related to the ability of this molecule to elicit direct leukocyte histamine release. However, there is evidence for IgE-mediated anaphylactic reactions based on skin tests and specific IgE assay (4,5). Recently, in a French study, thiopental has been reported as being involved in less than 1% of allergic reactions (6).

Since Cremophor EL, as a solvent for some non-barbiturate hypnotics, has been avoided, many previously reported hypersensitivity reactions have actually disappeared. In recent French surveys, reactions to propofol accounted for less than 2.5% of allergic reactions, and reactions to midazolam, etomidate or ketamine appear to be really rare as well (6,7). Finally, no immune mediated immediate hypersensitivity reaction involving isoflurane, desflurane nor sevoflurane has been reported despite the wide use of these drugs. Hypnotics may be skin tested according to the concentration limits provided in Table 1.

Opioids

Reactions to morphine, codeine phosphate, meperidine, fentanyl and its derivatives are uncommon. Morphine is known to induce histamine release; therefore, during skin testing, the maximal concentration recommended should not be exceeded (Table 1).

Because of the direct histamine releasing properties typical of opioids, distinction between anaphylaxis and non immune-mediated histamine release is not always easy. Only twelve cases have been recorded during the past 2 years in an epidemiologic survey conducted in France, nine of which being related to morphine administration (6). Skin prick tests, possibly followed, when negative, by intradermal tests, are performed with phenylpiperidines (alfentanil, fentanyl, remifentanil, sufentanil). Cross-reactivity remains uncommon among phenylpiperidines (8).

Local Anesthetics

Local anesthetics include amine (lidocaine, mepivacaine, prilocaine, bupivacaine, levobupivacaine, ropivacaine), and ester derivatives (chloroprocaine, procaine, tetracaine...). Allergic reactions to local anesthetics are very rare despite their frequent use and anaphylaxis has decreased in frequency because of the decreasing use of the ester group of local anesthetics. It is estimated that less than 1% of all reactions to local anesthetics have an allergy-mediated mechanism (9,10).

Inadvertent intravascular injection leading to excessive blood concentrations of the local anesthetic, or systemic absorption of epinephrine combined with the local anesthetic, are by far the most common causes of adverse reactions reported for these drugs. Sympathetic effects may include tremulousness, palpitations, tachycardia, diaphoresis, light-headedness, or near syncope. Although severe anaphylactic reactions have been reported with both types of local anesthetics, ester local anesthetics, with their structural benzoic acid ring and their ability to produce para-aminobenzoic acid-related metabolites, are more likely to provoke an allergic reaction, rather than amide local anesthetics. This common allergenic determinant implies cross-reactivity among local anesthetics belonging to the ester group, while cross-reactivity is rarely seen in-between the amide group and it is absent between esters and amides. Amides have been involved in less than 0.6% of the perioperative reactions (6). Allergy to local anesthetics may also be due to methylparaben, paraben or metabisulfite used as preservatives in commercial preparations.

Local anesthetics may be skin tested without preservatives or epinephrine, according to the concentration limits provided in Table 1.

Colloids

All synthetic colloids used to restore intravascular fluid volume have been shown to potentially cause clinical anaphylaxis. The overall incidence of reactions has been estimated to range between 0.033% (11) and 0.22% (12), and even a lethal outcome might be encountered. There are some differences between the allergic manifestations (skin, circulatory and respiratory system) and the severity of anaphylaxis due to reactions to colloids. Since the pathologic mechanisms leading to such reactions have not been fully elucidated yet, true prophylactic measures are still unknown. Therefore, it is mandatory to control the patient very carefully at the beginning of infusion; early symptoms of anaphylactic reactions should trigger immediate therapeutic measures. Studies of the adverse reactions to gelatin plasma substitutes have concluded that gelatins may initiate a life-threatening anaphylactic response (13). Allergic reaction to Hydroxyethyl starch (a colloid) has been reported during caesarean deliveries (14).

Gelatins and dextrans are more frequently incriminated in anaphylactic reactions than albumin or hetastarch. Direct release of histamine has been reported with urea-linked gelatine, antihistamine being efficient for the prevention of these reactions (15). Evidence for IgE mediated adverse reactions to gelatin have also been reported (12). In addition, adverse reactions to urea-linked gelatin (0.852%) seem to be more frequent than

with modified fluid gelatin (0.338%) (12), whereas IgG-mediated adverse reactions to hydroxyethyl starch are less frequent. Adverse reactions to dextrans are estimated to have an incidence of 0.275%, while the incidence is 0.099% for albumin and 0.058% for hydroxyethyl starch solutions (12). Skin tests may be performed with prick tests in pure solution, followed by intradermal tests in case of negativity.

Dye

Vital dyes have been used for many years in a variety of clinical situations and have long been considered a rare cause of anaphylaxis. This may be partially due to misleading nomenclature (16). Patent blue V (also called E131, Acid blue 3, Disulfine blue) and isosulfan blue (also called Patent blue violet or Lymphazurine), which belong to the group of triarylmethan dyes and share the same formula, are the most commonly used molecules (Figure 1). A Literature review may reveal an impressive number of case reports of hypersensitivity reactions (17), and it has been suggested that sensitization occurs using everyday products containing blue dyes. Considering the increasing use of blue dyes for lymphatic mapping for sentinel lymph node biopsy, the incidence of anaphylaxis to these drugs can be expected to increase.

The mechanism underlying the allergic reaction to patent blue remains unclear. Both direct mast cell and/or basophil activation and cross-linking of specific IgE antibodies are possible causative factors. Evidence supporting an IgE-mediated mechanism at least in some patients comes from two clinical reports, the first one demonstrating an immune mediated mechanism by a passive transfer test (18), the second one demonstrating the presence of specific IgE detected by an ELISA-test (19).

Methylene blue has also been shown to be an effective dye for sentinel lymph node localization, with only a limited number of complications reported. Anaphylactic reactions involving methylene blue seems to be very rare, probably since this small molecule does not bind to plasma proteins, thus reducing the risk of sensitization to an hapten-protein complex. This dye differs structurally from isosulfan blue and patent blue V. Therefore, cross-reactivity is not expected. However, several cases of sensitization to both patent blue and methylene blue have been reported, suggesting a possible immunologic cross-reactivity between these dyes (20,21). These reports support the systematic investigation of a possible cross-reactivity before the use of an alternate dye. A negative skin test with methylene blue in case of hypersensitivity reaction to patent blue V or isosulfan blue may induce to use methylene blue for future sentinel lymph node mapping.

The clinical diagnosis of reactions elicited by dyes is difficult. Reactions are usually long lasting and relatively delayed (i.e. thirty minutes after injection), and justify a prolonged follow-up in an intensive care unit, if prolonged epinephrine administration is necessary (20).

Dyes may be skin tested by prick tests followed by intradermal tests (with maximum dilution of 1/100 for the histamine-releaser methylene blue, and of 1/10 for isosulfan/ patent blue) (8).

NSAIDs

NSAIDs, including aspirin, may cause reactions, by inhibition of cyclo- oxygenase, resulting in generation of leukotriens. NSAIDs are increasingly recognized as a cause of non IgE-mediated anaphylactic reactions (22). They may be administered both during surgery and together with pre-medication, depending on the procedure. The onset of the reaction is usually up to 10 minutes after intravenous administration and 30-60 minutes after oral administration. If the reaction occurs at the end of surgery, induction agents may be immediately excluded, and the main differential diagnosis include reactions to NASIDs, latex or colloids. Clinical patterns of NSAIDs allergy include generalized pruritus, erythema, urticaria, angioedema, rhinorrhea, asthma and anaphylactic shock. Pyrazolones may precipitate reactions ranging from urticaria and angioedema to anaphylactic shock, presumably by immunological IgE-mediated mechanism. There are no reliable diagnostic tests for NSAID intolerance, so that the diagnosis remains essentially clinical, after having excluded other potential causes. However, the diagnosis can be confirmed by provocation test, but such procedure should be considered only when the history is not fully clear.

Iodinated Contrast Media

Iodinated contrast media (ICM) were introduced in the 1950s and are among the most commonly prescribed drugs. Severe and fatal reactions represent a serious problem, since more than 70 million applications of ICM are registered per year, worldwide.

ICM are among the most commonly used injectable drugs administered in radiology and they may be injected during surgical procedures as well. Modern ICM can be introduced in the body through different routes, such as intravenously, intra-arterially, intrathecally and orally (23). ICM hypersensitivity reactions can be either immediate or non-immediate (occurring up to the seventh day after the injection) in susceptible individuals. Mild immediate adverse reactions occur in 3.8- 12.7% and in 0.7- 3.1% of patients receiving intravenous injections of high-osmolar ionic and low-osmolar non-ionic ICM, respectively. Several immediate reactions have been reported in

Table 1. Maximal concentration for SPT and IDT (adapted from Mertes PM et al. Reducing the risk of anaphylaxis during anaesthesia: guidelines for clinical practice. *J Investig Allergol Clin Immunol* 2005;15:91-101)

DRUG	PRICK TEST		INTRADERMAL TEST	
		Maximal		Maximal
	Dilution	concentration	Dilution	concentration
		(mg/ml)		(µg/ml)
Hypnotics				
Etomidate	Undiluted	2	1/10	200
Midazolam	Undiluted	5	1/10	500
Propofol	Undiluted	10	1/10	1000
Thiopental	Undiluted	25	1/10	2500
Opioids				
Alfentanil	Undiluted	0.5	1/10	50
Fentanyl	Undiluted	0.05	1/10	5
Morphine	1/10	1	1/1000	10
Remifentanil	Undiluted	0.05	1/10	5
Sufentanil	Undiluted	0.005	1/10	0.5
Local anesthetics				
Bupivacaine	Undiluted	2.5	1/10	250
Lidocaine	Undiluted	10	1/10	1000
Mepivacaine	Undiluted	10	1/10	1000
Ropivacaine	Undiluted	2	1/10	200
Colloids				
Gelatin	Undiluted		undiluted	
Hydroxyethyl starch	Undiluted			
Dextran40/70	Undiluted	6-10	1/100	600-1000
Aprotinina	Undiluted	10000 IU/ml	1/100	100 IU/ml
Dyes				
Isosulfan	Undiluted	10	1/10	1000
Patent blue	Undiluted	25	1/10	2500
Methylene blue	Undiluted	10	1/100	100
ICM	Undiluted	300	1/10	30000
Chlohexidine	Undiluted	2%	1/100000	0.0002%

0.1- 0.4% and in 0.02-0.04% of patients, respectively. Although adverse reactions observed with non-ionic ICM are usually less severe than those with ionic ICM, their respective death rate does not significantly differ, being in the range of 1 each 100 000 examinations. Non-immediate hypersensitive reactions occur at various rates and they appear to be T cell mediated. Thus, they depend on the injected product and not on the osmolality, iodine content, or ionization of the drug (24).

Several studies have shown that skin tests are useful

tools for the diagnosis of ICM allergy, when the test is conducted within 2-6 months after the reaction, (25) and the negative predictive value of ICM skin tests is 96.6% (24).

Literature on secondary prevention by premedication is not clear enough to draw conclusions. The prophylactic use of corticosteroids and anti-histamines remain controversial, and premedication practice varies from country to country. Moreover, several anaphylactic reactions have been reported despite optimal

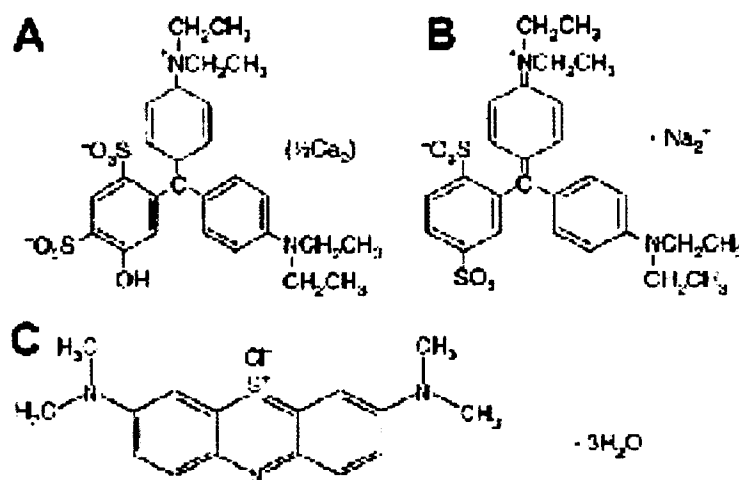


Figure 1. Structural formulas of dyes commonly used for sentinel lymph node localization: A, Patent Blue V; B, Isosulfan blue; C, Methylene blue.

pretreatment.

Antiseptics

Several cases of allergic reactions to antiseptics have been reported in Literature. They mainly concern allergic reactions to chlorhexidine after insertion of central catheters impregnated with this antiseptic, or after intraurethral use or topical application (26). Chlorhexidine is a synthetic cationic bis-biguanide, introduced in 1954, widely used as a disinfectant and antiseptic in medical and non-medical environments. Chlorhexidine may be found in many commercially available products, such as mouthwashes, antiseptic creams, and disinfectant solutions. In a medical environment, chlorhexidine is used in alcoholic or aqueous solutions for skin disinfection before invasive procedures, and as a disinfectant hand wash. Chlorhexidine is also present in potentially hidden forms, such as bactericidal coating for central venous catheters or as a component of urethral lubricants.

Chlorhexidine is a potentially immunogenic substance and may cause hypersensitivity reactions, such as contact dermatitis, contact urticaria or photosensitivity. Nevertheless, chlorhexidine may trigger allergic anaphylaxis as well. Several factors conspire to confound the clinical diagnosis of anaphylaxis to chlorhexidine, mainly a delayed presentation, or the fact that chlorhexidine is not a drug administered by an anaesthetist and that it may be present in a covert form. All these possible bias may bring to overlook anaphylaxis to chlorhexidine as a cause of cardiovascular collapse; symptoms related to chlorhexidine allergy may appear

up to 40 minutes after exposure (27). Only a few cases of anaphylaxis following topical use of povidone-iodine have been reported (6). Even though povidone-iodine is widely used as an antiseptic in surgery, IgE-mediated reactions are extremely unusual, with allergic contact dermatitis being the most common symptom (28).

Aprotinin

Aprotinin is a naturally occurring serine protease inhibitor. It is administered either intravenously, or as a component of biological sealants, because of its ability to decrease blood loss, and therefore transfusion requirements. IgG and IgE antibodies mediate anaphylactic reactions. The risk of anaphylactic reactions has been estimated between 0.5% and 5.8% when used intravenously during cardiac surgery, and in 5 out of 100,000 applications when used as a biologic sealant (29,30). Otherwise, in re-exposed patients, the risk of anaphylaxis to aprotinin is approximately 2.8%: patients previously treated with this drug present an increased risk of reaction, and any new administration should be avoided for at least 6 months after a previous exposure (31). Aprotinin has recently been withdrawn from the market for its use in reducing blood loss. However, some fibrin glue products still contain aprotinin (8).

Skin prick tests with pure solution followed by intradermal skin tests (with a dilution up to 1/10) in case of negativity are recommended, for diagnosis purposes.

Ethylene oxide and formaldehyde

Ethylene oxide (ETO), an alkylating compound of

high chemical reactivity, is widely used as a sterilization gas for various medical devices that are heat-sensitive, such as catheters, infusions sets, gloves, suture sets, surgical drapes and certain implantable materials such as ventriculoperitoneal shunts. This type of sterilization may cause rare but severe IgE-mediated allergic reactions, in sensitive patients, in particular in patients presenting with myelomeningocele or in hemodialysis, with a reported prevalence of sensitization in these groups of 23% and 12.1% respectively. In a Danish study, 201 patients presenting with symptoms ranging from mild skin symptoms to severe anaphylactic shock were investigated (32). Three patients (1.5%) had a history of anaphylaxis and presented high levels of sIgE to ETO, but had also another verified allergy to drugs or latex. Moreover, this study has showed that sIgE to ETO can vary over time. The fact that ETO is highly toxic, a hapten, and a gas, it makes it difficult to produce standardized material for skin tests, challenge studies, and *in vitro* tests.

Formaldehyde and paraformaldehyde are commonly used as denture base material and they can cause severe IgE mediated anaphylactic reactions. Symptoms may appear within several minutes or 1h after dental treatment, but they may even be delayed, appearing from 2 to 24 h after the treatment. The pathological reactions related to formaldehyde may be caused by simple irritant mechanisms. Formaldehyde in powder form or in aqueous solution may be more reactive than in gaseous form and may lead to sensitization in odonto-stomatology. Sensitization could result from domestic or occupational contact with formaldehyde (cosmetics, certain medicines, in dentists, anatomists, pathologists, etc) and especially after previous endodontic treatments.

Skin tests to formaldehyde are not standardized and may provoke delayed severe systemic reactions. Prick tests to 0.1 and 1% formaldehyde solution are often negative and are inconsistently positive to the pure solution used in dentistry. Specific IgE to formaldehyde may suggest underlying allergic mechanisms, but sometimes the presence of sIgE is not associated to clinical symptoms.

Protamine and heparins

Protamine, a low molecular weight protein, has been increasingly used during the last two decades and it may cause peri-operative reactions. When administered alone, protamine has an anticoagulant effect. When it is given in presence of heparin, both drugs lose their anticoagulant propriety, forming a stable salt.

Reactions may involve a number of mechanisms including IgE, IgG and the complement. In a recent review analyzing 9 retrospective studies and 16 prospective studies, the incidence of anaphylactic reactions was estimated to be 0.19% (retrospective studies) and 0.69%

(prospective studies), respectively (33). Protamine can cause significant histamine release resulting in hypotension and bronchospasm, and even pulmonary hypertension (34).

Skin tests with protamine may be helpful in identifying a possible IgE mediated response in selected cases. These tests must be interpreted with caution because they do not necessarily predict clinical sensitivity and do not identify all patients at risk. A sIgE protamine is available (34).

Heparins rarely have been identified as the cause of anaesthetic anaphylaxis.

Other agents

Allergic reactions following systemic administration of corticosteroids have rarely been reported in Literature and they mainly concern isolated cases. The allergic reaction may be caused by the steroid molecule itself, its ester or the excipients present in the preparation. Skin tests sometimes do not show an immunologic hypersensitivity mechanism and challenge tests are therefore necessary.

Hyaluronidase is a proteolytic enzyme that is sometimes used as a spreading factor to improve other drugs diffusion. Typical applications are as an adjunct to local anesthesia, especially in nerve blocks and ophthalmic anaesthesia. Hypersensitivity reactions to hyaluronidase induce local acute or delayed reactions. Diagnosis of IgE-mediated allergy to hyaluronidase can be confirmed by skin tests, quantification of sIgE or flow cytometry (34). Oxytocin is a synthetically manufactured hormone that stimulates contractions of the uterine smooth muscle and is indicated for induction and augmentation of labor as well as in abortions. Anaphylaxis from oxytocin is rare and diagnosis is generally based upon skin tests (34). To be noticed that, through a pharmacodynamical mechanism, oxytocin may produce hypotension which is not due to anaphylaxis.

CONCLUSIONS

Perioperative anaphylaxis remains a significant adverse event during anesthesia. Nevertheless, it remains underestimated because it is underreported. Neuromuscular blocking agents represent the most frequently involved substances, followed by latex and antibiotics, but each drug or substance used may be involved in an anaphylactic reaction. Diagnosis relies on specific tryptase measurements, skin tests, specific IgE or basophil activation assays.

A large number of clinical cases involving a wide variety of substances have been published in Literature. Moreover, since no premedication can effectively prevent an allergic reaction, any suspected hypersensitivity reaction must be extensively investigated using combined

peri and postoperative testing.

Patients must be fully informed of investigations results, and advised to provide a detailed report prior to future anesthesia. The wearing of a warning bracelet or possession of a warning card is strongly indicated.

With the exception of high risk patients, systematic preoperative screening for sensitization against anesthetic drugs is not justified at this time. Nevertheless, it is often difficult to determine the cause of anaphylaxis in such patients because they receive multiple medications within a short time, there are other exposures (e.g. latex, antiseptics) and allergy testing has limitations. Identification of the culprit agent can thus be a difficult challenge for allergists, but it remains essential to establish the cause of the reaction, in order to prevent future anaphylaxis.

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