

PERIOPERATIVE ALLERGY: RISK FACTORS

C. CAFFARELLI¹, G. STRINGARI¹, G. B. PAJNO², D.G. PERONI³, F. FRANCESCHINI⁴,
I. DELLO IACONO⁵, R. BERNARDINI⁶

¹*Pediatric Clinic, Department of Pediatrics, University of Parma, Parma, Italy;*

²*Allergy Unit, Department of Pediatrics, University of Messina, Messina, Italy;*

³*Department of Pediatrics, University of Verona, Verona, Italy;*

⁴*Pediatric Unit, "Ospedali Riuniti", University Hospital, Ancona, Italy;*

⁵*Pediatric Unit, "Fatebenefratelli" Hospital, Benevento, Italy;*

⁶*Pediatric Unit, "San Giuseppe" Hospital, Empoli, Florence, Italy.*

Perioperative anaphylactic as well as anaphylactoid reactions can be elicited by drugs, diagnostic agents, antiseptics, disinfectants and latex. In some individuals, allergic reactions occur in the absence of any evident risk factor. Previous history of specific safe exposure to a product does not permit to exclude the risk of having a reaction. We have systematically reviewed characteristics in the patient's history or clinical parameters that affect the risk of developing reactions during anesthesia. Evidence shows that patients with previous unexplained reaction during anesthesia are at risk for perioperative allergic reactions. An allergic reaction to an agent is associated with previous reaction to a product that is related with the culprit agent. Multiple surgery procedures, professional exposure to latex and allergy to fruit are associated with an increased frequency of latex allergy. It has been shown that in some instances, allergic perioperative reactions may be more common in atopic patients and in female.

The identification of patients at risk for allergic and pseudo-allergic reactions during the perioperative period is hampered by the fact that the cause of the reaction is not easy to establish. This depends on the large number of drugs, diagnostic agents, devices containing latex, antiseptics and blood products that are all routinely used in anesthesia. The low accuracy of diagnostic tests which is the consequence of the frequent non IgE-mediated mechanism of the reaction, also plays a part. About 60% of anaphylactic reactions during anesthesia are IgE – mediated. It is important to underline that a previous history of specific safe exposure to a product does not permit to exclude the risk of having a reaction. An uneventful exposure may sensitize an individual to subsequent administration (1). However, a systematic preoperative laboratory screening (e.g. specific IgE, Skin Tests) for the potential of anaphylaxis to products used during the perioperative period is not recommended in subjects with a negative history of reactions. This

is because there is a high frequency of false positive or negative IgE test results. Several factors have been associated with increased risk of developing reactions. High risk factors include allergy to a product used during anesthesia, previous anaphylaxis or severe reactions during anesthesia, and latex allergy.

ALLERGY TO PRODUCTS USED DURING ANESTHESIA

Some conditions or characteristics affect the risk of developing reactions during anesthesia (Table 1).

DRUGS

There is not enough evidence that allergic reactions to anesthetic drugs are associated with previous reactions to a drug that is unrelated with those used during the course of anesthesia, with rare exceptions (e.g. colloids).

Key words: Allergy; Anaphylaxis; Anesthesia; Bronchial asthma; Hypersensitivity; Contrast media; Risk factors; Drug intolerance.

Correspondence address: Carlo Caffarelli, MD
Pediatric Clinic, Department of Pediatrics, University
of Parma, Via Gramsci 14,
43126, Parma, Italy.
Phone: +39.0521.70220 Fax: +39.0521.702830
E mail: carlo.caffarelli@unipr.it

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Neuromuscular blocking agents (NMBA)

Neuromuscular blocking agents (NMBAs) are the drugs mostly involved in anaphylaxis. An IgE mediated mechanism is responsible for 60% of the reactions. Cross-sensitivity between NMBAs has been reported to be about 65% by skin tests and 80% by radioimmunoassay inhibition tests, which is considered the result of the shared tertiary or quaternary ammonium groups. However, it is unusual that an individual reacts *in vitro* to all NMBAs (2-4). The cross-reactivity between NMBAs has also been demonstrated clinically. In patients with a severe reaction to one or more muscle relaxants, subsequent administration of NMBAs was associated with clinical hypersensitivity reactions, ranging from anaphylaxis to minor adverse events, in about 15% of cases (5). Therefore, an anaphylactic reaction to a muscle relaxant is a positive risk factor for an allergic reaction to different NMBAs in future anesthesia.

Reactions to muscle relaxants may develop at the first exposure. This may happen when a subject has been previously sensitized to cross reacting substances containing quaternary or tertiary ammonium ions such as other classes of pharmaceuticals including acetylcholine, choline, morphine, neostigmine, pentolinium and pholcodine (PHO) (1), cosmetics or detergents. There is no clear evidence that NMBAs cross react with propofol (6).

A multicenter study conducted by Johansson and coworkers (7) assessed the relationship between the use of cough-relieving medicine containing PHO and the levels of IgE antibodies to PHO, morphine and suxamethonium in nine countries. The prevalence of patients sensitized to PHO, morphine and suxamethonium varied from less than 1% in countries (Denmark, Finland, Germany, Netherlands, Sweden, US) with low consumption of drugs with PHO to 2.4% -7.0 % in countries (France, Norway, UK) where the consumption of drugs with PHO was high. In countries where the PHO containing drugs were not used, the detection of IgE antibodies to NMBAs might be associated with exposure to ammonium groups of personal care products. Previous studies have shown that serum IgE antibodies to PHO (ImmunoCAP Allergen c261 Pholcodine) were a risk factor for adverse reactions to rocuronium, with a sensitivity of 86% and a specificity of 100% (8). While sensitivity of IgE to rocuronium, suxamethonium, morphine was respectively 68%, 60%, 88%, specificity was 100% for suxamethonium, morphine and 93% for rocuronium. These data may indicate that PHO hypersensitivity reflects the sensitization to ubiquitous quaternary ammonium ions. Most anaphylactic reactions to NMBA develop in females. This suggests a role for potentially cross-reacting ammonium structures in detergents or cosmetics. Considering these data, it has

been suggested that a history of sensitivity to cosmetics or cough medicines may raise caution in the use of NMBA (1).

Antibiotics

Among antibiotics, penicillin and cephalosporin elicit approximately 70% of perioperative anaphylactic reactions (4). In patients with allergy to penicillin there is a 3-10% risk of reaction after cephalosporin administration because they have a similar beta-lactam ring. Further cross reacting antibiotics with a β -lactam ring are piperacillin, ticarcillin, aztreonam, ertapenem, imipenem, and meropenem. Risk factors for an allergic reaction to penicillin or cephalosporin are a positive history of reaction and a positive skin test. Penicillin skin testing identifies patients with clinical hypersensitivity reactions in about 70% of cases (9). Allergic reactions to other antibiotics, including vancomycin, bacitracin, clindamycin, gentamicin, and metronidazole are uncommon. It is unclear whether skin test results predict reactions to such antibiotics.

Induction drugs

Barbiturates, especially thiopental can be the responsible for perioperative anaphylaxis. The reactions to thiopental are commonly IgE-mediated. Risk factors for having an adverse event are previous exposure to the drug or female gender (10). *In vitro* studies revealed that cross-reactivity occurs between serum IgE antibodies to thiopental and four barbiturate analogues, pentobarbitone, phenobarbitone, barbitone and methohexital (11). The clinical significance of such finding is unclear. Until now methohexital has been reported to provoke only non IgE-mediated reactions.

Propofol (2-6 diisopropylphenol) is an alkyl phenol in a lipid vehicle (soybean oil, egg lecithin, and glycerol). A child with multiple food allergies including egg and peanut was reported to have an anaphylactic reaction after administration of propofol. However the child concomitantly received other drugs including rocuronium (12). Different explanations may be offered for this case report. Cross-reactivity between soybean oil and peanut that belongs to the legume family (Fabaceae) may explain why patients with peanut allergy have had anaphylactic reactions when propofol was administered (13). However, patients with peanut allergy generally tolerate soy, suggesting that cross reacting serum IgE antibodies revealed by inhibition assays are not clinically relevant. Furthermore, the soy oil that is contained in propofol is refined and does not include significant quantities of allergenic particles (14). Egg lecithin is a minor allergen that rarely causes allergic reactions in subjects with egg allergy. Its amount in propofol vehicle is very low. Skin

tests with propofol or with its lipid vehicle have been reported to be negative in patients with egg allergy (15). Propofol is currently used in patients with soy allergy without any reactions (4). Therefore, there is no sufficient evidence that propofol is more likely to provoke allergic reactions in subjects with egg allergy (1).

Etomidate, ketamine. Adverse reactions to these drugs that are chemically unrelated to other hypnotics, are very uncommon. It has been suggested that atopy can favor the non specific release of histamine, and this may predispose to anaphylactic reactions after administration of ketamine (16).

Benzodiazepines (diazepam, midazolam). Allergic reactions to diazepam are often caused by the propylene glycol solvent. Thus, a history of symptoms suggestive of allergy to products containing this solvent such as medications, vaccines, cosmetics, and foods should be considered a risk factor for the onset of reactions to diazepam. IgE-mediated reactions to diazepam have been attributed to the active metabolite desmetyldiazepam which is an antigenic molecule and seems to be responsible for the cross reactivity with other benzodiazepines. Midazolam does not have active metabolite. No specific risk factors have been identified for reactions to midazolam.

Opioids

Allergic reactions to opioids are uncommon (1) and usually result from nonspecific mast cell activation, rather than from IgE-mediated degranulation (4). Fentanyl does not induce non-specific histamine-release (8). Some case reports of anaphylaxis caused by fentanyl, meperidine, morphine, and codeine have been described. There is no clinical cross-reactivity between different subclasses of opioids. Consequently, patients with reaction to phenanthrenes (morphine, codeine), are not at risk of having reactions following the administration of a phenylpiperidines (fentanyl, alfentanyl, meperidine). The predictive value of skin testing with morphine is unknown.

Non-steroidal anti-inflammatory drugs (NSAIDs)

NSAIDs can cause reactions, by inhibiting cyclo-oxygenase I enzyme (COX-1) or cyclo-oxygenase II enzyme (COX-2) that leads to the production of leukotrienes. Cross reactivity among COX-1 inhibitors is common, but it occurs less frequently between acetaminophen and nimesulide. Among COX-2 inhibitors clinical cross reactivity is also frequent. Allergic reactions to COX 1 inhibitors are risk factors for reaction to COX 2 inhibitors.

Local anesthetics

Anaphylactic reactions to local anesthetic drugs are

unusual (1). Local anesthetics are classified as amides or esters. Patients allergic to drugs belonging to the benzoic acid ester group (benzocaine, procaine, propoxycaine, tetracaine), are at risk of allergic reactions with drugs from the same family since cross reactivity is frequent. This cross reactivity also occurs to a lower degree among members of the amide class (lidocaine, mepivacaine, bupivacaine, articaine, dibucaine). Cross reactivity between benzoic acid ester and amide group has not been reported (17).

Colloids

Colloids (plasma volume expanders) used in the perioperative period include gelatin, albumin, hydroxyethyl starch (HES), and dextrans. They are responsible for approximately 4% of all perioperative anaphylactic reactions (1). Allergic reactions to colloids are more common in males and in subjects with multiple drug allergies (18). Gelatin is a protein produced by hydrolysis of cattle or pork collagen. It is contained in a great variety of foods, vaccines, pharmaceuticals and cosmetics. Therefore, patients with a history of allergic reactions to products with gelatin should be considered at risk of perioperative anaphylaxis. The administration of albumin is considered safe in patients with egg allergy (19).

Other agents

Previous exposure to protamine, medication allergy, vasectomy and fish allergy has been reported to be associated with allergic reactions to *protamine* (20-25). Allergic reactions to *aprotinine*, a polypeptide derived from bovine tissue, have been associated with previous administration of the drug (from 15 days to 6 months before), beef, egg or cow's milk allergy and pancreatitis. We are not aware that risk factors have been identified for reactions to *hyaluronidase*, *oxytocin*, *methylmethacrylate* (bone cement). Patients with IgA deficiency develop reactions when they receive IgA with *blood transfusions* because they can produce IgE or IgG antibodies against IgA.

DIAGNOSTIC AGENTS

Dyes

Blue dyes are used as tracers in lymphangiography, cardiac output determination and sentinel lymphadenectomy in a variety of neoplasms. Patent blue is also used in the textile and paper industry, cosmetics, and as antibacterial and antifungal agents. It has been suggested that everyday exposure to products containing blue dyes may induce sensitization. Patients who react to patent blue are at risk of having reactions to isosulfan

blue since these dyes have same formula and cross-sensitization occurs commonly (26, 27).

Methylen blue differs structurally from Patent Blue V (28). However, cross-sensitization between these dyes has been reported (29). Therefore it remains uncertain whether methylen blue giving rise to a positive skin test is safe in patients with allergy to Patent Blue V.

Two cases of IgE-mediated anaphylaxis to methylene blue have been reported (30, 31). In one case, the patient had never had previous contact with methylene blue. Therefore, the authors hypothesized that the dyes contained in other drugs may have sensitized the patient. Keller and coworkers (32) found positive skin prick test to methylene blue in patients that had never been exposed to it, with a hypersensitivity reaction to patent blue. Preformed IgE antibodies, originally directed to another antigen, may have caused the allergic reaction to methylene blue at the first known exposure.

Radiographic Contrast Material (RCM)

The administration of an ionic RCM similar to that which provoked an adverse reaction is a risk factor for a successive immediate reaction (6, 33-37). The rate of such reactions has been reported to vary from 16% to 44%. In patients with allergy to high osmolarity RCM, the administration of low osmolarity RCM is also a risk even if it is associated with a 10-fold lower number of adverse effects. Risk factors for an immediate reaction to ionic RCM include cardiac disease, food allergy, bronchial asthma (38) or treatment with β -blockers (39). Questionnaire surveys have shown that the occurrence of delayed reactions to RCM are associated with previous severe reactions to RCM, serum creatinine > 2 mg/ml, history of drug and contact allergy (40) and therapy with Interleukin-2 (41). Factors that may influence the severity but not the onset of the reactions to RCM, include mastocytosis, viral infection at time of RCM administration and autoimmune diseases, such as LES (42, 43). The allergenicity of RCM is not related to the iodine content. Thus, patients with adverse reactions to topically applied iodine-containing solutions (e.g. povidone-iodine) or to seafood containing inorganic iodine are not at risk for adverse events from iodinated RCM (44). Dosage or concentration of RCM administered are not related with the development of reactions.

Gadolinium

A previous allergic reaction to iodinated contrast agent is a risk factor for adverse reactions when gadolinium is administered (45).

Antiseptics and disinfectants

Despite of the ubiquitous use, antiseptic and

disinfectant allergy is uncommon.

Chlorhexidine can induce contact dermatitis; it has been reported that it may precede the development of chlorhexidine-induced anaphylaxis by years. Therefore, it has been suggested that patients with a diagnosis of contact dermatitis to chlorhexidine are at risk for anaphylactic reactions to this antiseptic (46).

Povidone-iodine (betadine) is an advantageous option since it rarely causes IgE mediated anaphylaxis. Skin testing, but not patch testing that may give false-positive results, is a predictive factor.

LATEX ALLERGY

Latex is the second most common cause of anaphylaxis during anesthesia in the general population (15). Children with IgE-mediated clinical reactions to latex account for about one fifth of intra-operative anaphylaxis. It is worth to note that in about 20% of subjects with reactions during the perioperative period, a careful assessment of medical history revealed the presence of previous symptoms suggestive of latex sensitization such as intolerance to materials containing rubber latex (47).

There are some groups of children that are at risk of allergic reactions to latex during the perioperative period (4). The major group consists in children who were significantly exposed to latex because they required multiple surgical procedures (e.g. spina bifida, spinal cord trauma, urogenital malformations). Some children have a genetic predisposition to latex allergy because of atopy or allergy to certain fruits (avocado, kiwi, banana, fig, chestnut, hazelnut, sweet pepper, melon, pineapple, papaya, and others) which immunologically cross react with latex (latex-fruit syndrome) (48). Patients with positive skin tests to latex but without a history of clinical hypersensitivity reactions are not at risk when they suffer from pollinosis or are monosensitized to latex profilin (Hev b 8).

Furthermore, workers such as healthcare professionals and employees of the rubber industry, are likely to develop latex allergy because of occupational exposure.

Previous perioperative reactions

The ascertainment of an allergic reaction during anesthesia is not easy. Diagnosis is not obvious since symptoms of allergic reactions can also occur as a result of an interaction between the clinical status of the patient, the drugs and common side effects of anesthesia (49). Another difficulty in the diagnosis of anaphylactic perioperative reactions comes from the inconsistency with allergic reactions in the real life. Skin symptoms are lacking in one-third of the cases and hypotension or bronchospasm may occur as an isolated condition.

Table 1. Factors favoring reactions to products used in the perioperative period.

Agent	High risk factors	Low risk factors
NMBA	• Previous reaction to other NMBA's	• Allergy to cosmetics or detergents • Sensitization to Pholcodine (cough relieving medicine)
Cephalosporins, β -lactam antibiotics	• Penicillin or β-lactam antibiotics	
Thiopental		• Previous exposure • IgE to other barbiturates
Propofol		• Allergy to egg, peanut and soy (not clear evidence) • Atopy
Ketamine		• Atopy
Benzodiazepines	• Reaction to other benzodiazepines • Allergy to propylene glycol solvent	
Opioids	• Reaction to drugs of the same subclass (phenanthrenes or phenylpiperidines)	
NSAID	• Previous reaction to NSAIDs	
Local anesthetics	• Reaction to drugs belonging to the same subclass (benzoic acid ester group or amides)	
Colloids	• Gelatin allergy	• Multiple drug allergy • Male gender
Protamine		• Previous exposure • Drug allergy • Vasectomy • Fish allergy
Aprotine		• Previous exposure • Allergy to beef, cow's milk and egg • Pancreatitis
Blood transfusion	• IgA deficiency	
Patent blue	• Previous sensitization to isosulphane blue	
Radiographic contrast material (RCM)	• Previous reaction to RCM ionic and non ionic	• Atopy • For immediate reactions: cardiac disease, therapy with β – blockers, food allergy and bronchial asthma • For delayed reactions: serum creatinine > 2 mg/ml, previous reaction to RCM, history of drug and contact allergy and IL-2 treatment
Gadolinium	• Reaction to RCM	
Chlorhexidine	• Contact dermatitis to chlorhexidine	
Latex	• Multiple surgical procedures (i.e. spina bifida) • Professional exposure to latex (Health care or rubber industry workers) • Allergy to fruits	• Atopy
All agents	• Previous unexplained reaction during anesthesia. • Diagnosis of allergy to the agent.	• Female gender (except colloids)

Furthermore, the cause-effect relationship is difficult to prove since many reactions derive from non-IgE mediated mechanisms and this may lead to a negative result of IgE tests.

Moreover, during the perioperative period, patients are exposed to a large number of potential allergens, thus making the identification of the causative agent difficult. Therefore, a history of anaphylaxis or of a severe undiagnosed adverse event during a previous anesthetic is a risk factor for allergic reactions during anesthesia.

Other risk factors

Atopy is an hereditary predisposition to produce IgE to environmental allergens, such as aeroallergens and foods. Atopy may be associated with both occurrence of allergic reactions during anesthesia and their increased severity. There is evidence that atopic subjects are more likely to have allergic reactions to latex (48), propofol (50), ketamine (16) and contrast media (51). Atopy has been suspected to be a risk factor for muscle relaxant sensitization. However, symptoms suggestive of atopy, skin tests and specific IgE to common aeroallergens were similar in patients who reacted to NMBAs in comparison with those who did not react (52). Moreover, the prevalence of atopy defined by the presence of at least one positive skin test and/or the presence of IgE antibodies against at least one aeroallergen, did not differ between subjects with allergic reactions to NMBA and control subjects.

It is unclear whether atopic asthma constitutes a risk for allergic reactions during the perioperative period. There are some data that suggest that perioperative allergic reactions are more common in children with asthma. It has also been shown that patients with asthma are more likely to have latex allergy (47).

Perioperative anaphylaxis is more frequent in *females* rather than in males, with a 3:1 ratio (53), ranging from 8 females:1 male for NMBAs to 2.7 females:1 male for thiopental. This is particularly the case when there are reactions to muscle relaxant and latex.

Skin disorders such as *mastocytosis* and *chronic urticaria- angioedema* have been considered to be risk factors because they are associated with an increased release of mediators of the allergic reaction. However, there is a low prevalence of clinical hypersensitivity reactions in children with mastocytosis. Sparse data do not allow to exactly analyze this risk (54).

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