■ CLINICAL CONCEPTS AND COMMENTARY

Bruno Riou, M.D., Editor

Anaphylaxis and Anesthesia

Controversies and New Insights

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PERIOPERATIVE anaphylaxis may be a life-threatening clinical condition and is typically a result of drugs or substances used for anesthesia or surgery. After anaphylaxis, allergologic assessment is essential to identify the offending agent and prevent recurrences, because no preemptive therapeutic strategies exist. This review seeks to (1) identify the clinical diagnostic pathway necessary to distinguish anaphylaxis from confounding clinical diagnoses, (2) discuss the more common allergens that cause anaphylaxis during anesthesia, (3) discuss a rational approach to the identification of the offending allergen through blood and skin testing that allows for the safe future clinical management of patients experiencing perioperative anaphylaxis, and (4) discuss new therapeutic perspectives for the management of patients whose hemodynamic collapse is unresponsive to catecholamines, the initial recommended pharmacologic intervention.

Pathophysiologic Elements

Anaphylaxis occurring during the perioperative period is a clinical syndrome involving multiple organ systems. The clinical manifestations are the consequences of the immediate as well as ongoing release of preformed mediators from mast cells and basophils. Careful consideration must therefore also be given to the monitoring of the patient after the management of anaphylaxis.[1,2]

In the early 2000s, the European Academy of Allergology and Clinical Immunology proposed to define this acute nosologic entity as "a severe, life-threatening, generalized or systemic hypersensitivity reaction,"[3] primarily mediated by type E immunoglobulins (IgEs). More recently, this clinical entity was defined by the second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network symposium as follows: "Anaphylaxis is a serious allergic reaction that is rapid in onset and may cause death."[4] The European Academy of Allergology and Clinical Immunology committee recommended that the term *anaphylactoid*, introduced for non–IgE-mediated anaphylactic reactions, should no longer be used,[3] but this proposal has not been universally accepted.[4]

Classically, IgE isotype antibodies are produced on an initial exposure to an allergen in susceptible individuals and bind to high-affinity $F_C\varepsilon RI$ receptors located in the plasma membrane of tissue mast cells and blood basophils, whereas lymphocytes, eosinophils, and platelets bind IgE antibodies *via* low-affinity $F_C\varepsilon RII$ receptors. This initial phase of sensitization is clinically silent. On reexposure, the multimeric allergen cross-links two specific IgE receptors, creating a bridge between two IgEs. The two IgE receptors aggregate and induce a signal transduction cascade releasing systemically preformed biochemical mediators, including histamine, neutral proteases (tryptase, chymase), and proteoglycans (heparin) from intracellular granules in cells within tissues and blood. Some of these mediators, such as histamine, lead to increased nitric oxide production.[5] Newly formed proinflammatory phospholipid-derived mediators, including prostaglandin D_2, leukotrienes, thromboxane A_2, and platelet-activating factor, are released soon after. Thereafter, mast cells release numerous chemokines and cytokines that initiate recruitment and activation of additional inflammatory cells.

One key issue of anaphylaxis is that a very small amount of allergen is sufficient for the cells to react. The involved target organs commonly include the skin, mucous membranes, cardiovascular and respiratory systems, and the gastrointestinal tract. The corresponding

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Table 1. Clinical Severity Scale of Immediate Hypersensitivity Reactions Adapted from *Ring and Messmer*[6]

Grades	Clinical Signs
I	**Cutaneous-mucous signs:** erythema, urticaria with or without angioedema
II	**Moderate multivisceral signs:** cutaneous-mucous signs ± hypotension ± tachycardia ± dyspnea ± gastrointestinal disturbances
III	**Life-threatening mono- or multivisceral signs:** cardiovascular collapse, tachycardia, or bradycardia ± cardiac dysrythmia ± bronchospasm ± cutaneous-mucous signs ± gastrointestinal disturbances
IV	**Cardiac arrest**

clinical signs are erythema, edema, pruritus, arterial hypotension, tachycardia, and bronchial and gastrointestinal smooth muscle constriction, described by the Ring and Messmer clinical severity scale, which was adapted to describe perioperative immediate reactions (table 1).[6] Although this scale does not take into account the pathophysiologic mechanisms, it is appropriate for grading the clinical severity and guiding the clinical care of immediate reactions.[1,7] *In vivo* and *in vitro* procedures can be used to differentiate between allergic (where an immune mechanism can be demonstrated, *i.e.*, an anaphylactic mechanism) and nonallergic (also previously called *anaphylactoid*, where an immune mechanism is ruled out) hypersensitivity reactions.

Epidemiology

The overall incidence of perioperative anaphylaxis is estimated at 1 in 10,000–20,000 anesthetic procedures, whereas it is estimated at 1 in 6,500 administrations of neuromuscular blocking agents (NMBAs).[8] Its exact incidence remains underestimated as reactions are underreported.

Anaphylaxis is one of the rare clinical events specifically related to anesthesia leading to perioperative morbidity and mortality. Morbidity remains unknown. In France, 3% of the deaths that are partially or totally anesthesia related involve anaphylaxis,[9] whereas 10% of perioperative immediate hypersensitivity reactions reported to the United Kingdom Medicines Control Agency are fatal.[2] Nevertheless, this latter datum should be interpreted cautiously because many less severe reactions are probably not reported.[2]

In France, NMBAs were shown to be the most common agents involved, followed by latex and antibiotics.

In a Norwegian single-center study, NMBAs were most commonly involved, with latex implicated in very few cases and with no causal agent identified in one third of the cases.[10] Conversely, in two Spanish centers, antibiotics followed by NMBAs were the main agents involved.[11] Anaphylaxis to NMBAs is not uncommon in patients without any known previous exposure to any NMBA.[2,11] In this particular clinical setting of anaphylaxis after a first-time NMBA administration, the source and the nature of the sensitizing agent remain unknown.[12] However, quaternary ammonium ions are suggested to be the allergenic determinants in NMBAs.[12] Commonly used chemicals, such as toothpastes, detergents, shampoos, and cough medicines, share these determinants with NMBAs. In a predisposed individual, these common chemicals might be one of the contributing factors promoting sensitization to quaternary ammonium ions and creating the risk for developing anaphylaxis to NMBAs.[2] Recently, it has been suggested that the sensitization to quaternary ammonium ions seems to be related to exposure to pholcodine, a cough-relieving medicine.[12] Moreover, an individual can have uneventful previous exposures to a specific drug (*e.g.*, NMBAs, antibiotics), which does not preclude the risk of anaphylaxis after a subsequent administration of this drug.[2]
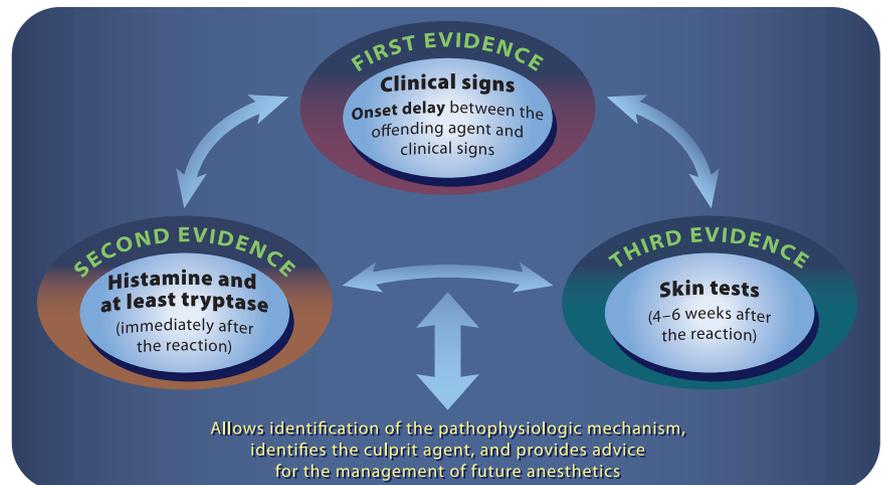
How to Diagnose Perioperative Anaphylaxis?

The etiologic diagnosis of an immediate reaction occurring during anesthesia relies on a triad including clinical, biologic, and allergologic evidence (fig. 1).

First Evidence: The Clinical History Is Crucial

The initial diagnosis of anaphylaxis is presumptive, although essential, because anaphylaxis may progress within minutes to become life-threatening. The first line of evidence for the diagnosis of anaphylaxis includes the features and severity of clinical signs and the timing between the introduction of a suspected allergen and the onset of symptoms, whereas the required dosage for resuscitative medications gives insight as to the severity of the reaction.[1] The clinical features occurring during anesthesia may involve cardiovascular symptoms (tachycardia, bradycardia, cardiac arrhythmias, hypotension, cardiovascular collapse, cardiac arrest), bronchospasm, and cutaneous–mucous signs (erythema, urticaria, angioedema).[1,2,7,8] They are described according to the Ring and Messmer four-step grading scale adapted as follows (table 1).[1,6,7] Grade I involves cutaneous–mucous signs, whereas grade II corresponds to mild cutaneous–mucous features that may be associated with cardiovascular and/or respiratory signs. The cardinal sign of grade III is cardiovascular collapse that may be associated with cutaneous–mucous signs and/or bronchospasm, and grade IV is cardiac arrest. Grades I and II are usually not life-threatening conditions, whereas grades III and IV cor-

Fig. 1. The etiologic diagnosis of periop- erative anaphylaxis relies on a triad in- cluding clinical, biologic, and allergo- logic evidence.

respond to emergency situations necessitating prompt resuscitation.

Perioperative anaphylaxis usually occurs within min- utes, even 1 min, after anesthetic induction and is pri- marily linked to agents administered intravenously.[1] The most commonly reported initial clinical features during severe reactions (grade III or IV) are pulselessness, de- saturation, and difficult lung inflation due to severe bron- chospasm. Respiratory signs are enhanced in patients with underlying asthma and/or chronic obstructive pul- monary disease. Asthmatic patients experiencing periop- erative anaphylaxis are therefore more likely to exhibit bronchospasm.[1,2] Cardiovascular symptoms often in- clude hypotension and tachycardia but may rapidly progress into severe arrhythmias and cardiovascular col- lapse if not recognized and treated in a timely fashion.[1] Because cardiovascular disturbances are the hallmark of severe anaphylaxis, cardiovascular collapse as the sole feature or cardiac arrest may be the inaugural event.[1,2,7,8] Acute coronary events associated with hy- persensitivity reactions were recently referred to as *Kou- nis syndrome*, which is also called *allergic angina* or *allergic myocardial infarction*.[13] Two variants were described as the consequences of mast cell mediator release: type I includes patients without predisposing factors for coronary artery disease, whereas type II in- cludes patients with predisposing factors. The allergic reaction may induce coronary artery spasm with normal cardiac-specific enzymes in variant I, whereas acute in- farction may be seen in both groups (types I and II). A threshold level of mast cell content has been suggested to be involved in the occurrence of such events.[13]

Predictive Criteria of Anaphylaxis Severity. Three predictive criteria of the severity of an ongoing anaphy- lactic reaction, which may or may not be associated, include the following: (1) The more rapidly anaphylaxis occurs after allergen exposure, the more likely the reac- tion is to be severe and potentially life-threatening.[14] (2) Cutaneous signs may be absent in rapidly progressive anaphylaxis.[14] Accordingly, the subcutaneous vascular

bed is susceptible to vasoconstrictive influences during anaphylaxis (being the first vascular bed compromised when circulatory homeostasis is threatened). Cutaneous signs may therefore only appear after the normalization of blood pressure. Consequently, the absence of initial cutaneous vasodilatation should not preclude the diag- nosis of anaphylaxis. (3) Another potentially confound- ing sign might be bradycardia, which can be seen in massive hypovolemia, probably as a result of the Bezold– Jarisch reflex, a cardioinhibitory reflex that has its origin in sensory receptors of the left ventricle transmitted by unmyelinated vagal C fibers.[14] This paradoxical brady- cardia occurring during extreme hypovolemia has been reported to occur in as many as approximately 10% of patients with anaphylaxis during anesthesia.[2] In this case, bradycardia may be considered as a life-protecting adaptive mechanism that allows the ventricles to fill before they start contracting again despite a massive hypovolemia. Therefore, this specific event during ana- phylaxis must be recognized by the anesthesiologist car- ing for the patient because the administration of atro- pine in direct response to the symptom of bradycardia might directly induce a circulatory arrest, the adequate treatment in this setting being a large volume expansion followed by epinephrine.

Which Drugs or Agents? The most commonly in- volved agents in perioperative anaphylaxis are NMBAs, latex, and antibiotics. Anaphylaxis usually occurs shortly after induction,[1,7] with NMBAs or antibiotics being pri- marily involved,[7] but anaphylaxis may occur any time with all potentially allergenic agents.[1] Dyes, hypnotic agents, local anesthetics, opioids, colloids, aprotinin, protamine, chlorhexidine, and contrast agents are less frequently involved.[1,2,7] Latex-induced anaphylaxis usu- ally occurs up to 30–60 min after the beginning of the surgery but may occur immediately.[2,15] Severe and even fatal reactions to latex are now reported.[16] Attempts to ban latex from use in clinical products is therefore en- couraged because the incidence of latex-induced anaphy- laxis has increased dramatically during the past two de-

cades, especially in high-risk groups of patients such as children or adults requiring multiple surgical procedures or healthcare workers.[17] Anesthesiologists themselves have a high prevalence of latex sensitization, which may have a genetic basis.[18] Accordingly, in a pediatric hospital including operating rooms and perioperative care areas, no allergic reaction to latex has been reported in 25,000 anesthetized children or in healthcare workers when a latex-free environment policy has been adopted.[17]

Finally, the onset and type of symptoms depend on the allergen concentration,[19] whereas the length of symptoms (up to 36 h) may vary according to the mode of injection (*e.g.*, when using dyes such as isosulfan blue or patent blue for lymphatic mapping and sentinel lymph node biopsy). Moreover, the patient's sensitivity level and route of administration are important in determining the onset and severity of symptoms. For example, intravenous and mucous membrane exposure are likely to be associated with a faster onset of more severe symptoms.[19]

Second Evidence: Biologic Assessment Contributes to the Diagnosis

Biochemical tests are available, either *in vivo* or *in vitro*.

Primary Investigation. Histamine is a preformed inflammatory mediator contained in granules of mast cells and basophils. An early increase in plasma histamine concentration indicates activation of mast cells and/or basophils and is observed during allergic or nonallergic mechanisms. Conversely, the absence of histamine increase does not preclude an immunologic or nonimmunologic mechanism. The plasma half-life of histamine is assumed to be very short (15–20 min).[7] Blood samples for histamine measurement should therefore be drawn within 30 min after a grade I or II reaction. After severe reactions (grades III and IV), histamine may still be increased 2 h after the reaction, probably because of the saturation of the enzymatic metabolism of histamine allowing for the detection of increased histamine levels for this prolonged period after the reaction.[7]

Tryptase is a mast cell neutral serine protease and a preformed enzyme. Two major forms have been identified[2,20]: α-Tryptase is secreted constitutively and is increased in mastocytosis, whereas pro–β-tryptase also secreted constitutively serves as a measure of mast cells mass. Mature β-tryptase is preferentially stored in mast cells granules and, when systemically released, reflects mast cell activation with mediator release.

Serum tryptase concentrations reach a peak between 15 min and 1 h and decline under apparent first-order kinetics with a half-life of approximately 2 h.[1,2,7] Therefore, blood samples may be drawn within 15 and 60 min in grade I or II reactions and within 30 min and 2 h in grade III or IV reactions.[1,7] An increase of total tryptase concentrations (*i.e.*, the sum of α- and β-tryptase) is highly suggestive of mast cell activation as seen in ana-

phylaxis, but its absence does not preclude the diagnosis (grades I and II). Conversely, an increase of tryptase may be seen during nonallergic mechanisms, although less pronounced when compared with immunologic mechanisms.[2,20] To compare the concentrations with baseline levels, a new sample of tryptase can be taken either at least more than 24 h after the reaction or when the patient is referred for investigation.[1,7,20] Finally, tryptase concentrations may remain increased in cases of late-onset, biphasic anaphylaxis or when associated with an underlying mastocytosis[2,19,20] (fig. 2).

In clinical situations of an immediate nonallergic reaction (*e.g.*, histamine release), histamine may be increased, whereas tryptase usually remains normal. In contrast, because histamine and tryptase concentrations correlate with the severity of the allergic reaction,[7] combined histamine and tryptase measurements have been recommended for the diagnosis of immediate reactions,[7] whereas others recommend only tryptase.[1,2,20] This constitutes the second component of the triad.

Secondary Investigation. Other *in vitro* tools have been proposed in clinical practice but are not available everywhere. No NMBA-specific IgE assay is currently available, except for suxamethonium, and its sensitivity remains low (30–60%).[20] Some authors suggested the use of a quaternary ammonium (choline analog) or morphine-based solid-phase IgEs to evaluate sensitization to the quaternary ammonium of NMBAs.[12,20] *In vitro* specific IgE assays are also available for a few other anesthetics (thiopental, propofol), antibiotics (amoxicillin, cefaclor, penicillin G and V), or latex.[2,7,20] Nevertheless, specific IgE assays seem to be less sensitive than skin tests.[12] Finally, serum IgEs provide a possible explanation of the mechanism but do not prove that the drug or agent is responsible for the reaction.[2]

Several other tests are proposed for the indirect detection of specific IgEs to anesthetic drugs. The leukocyte histamine release test is reliable when cross-reactivity among NMBAs is investigated for NMBA reintroduction.[1,7] The quantification of *in vitro*–activated basophils (CD63 and CD203c) after challenge with the culprit agent using flow cytometric analysis might be a useful tool for the diagnosis of NMBA-induced anaphylaxis[1,2,20] but requires further investigation.

Third Evidence: Skin Tests

Skin tests remain the gold standard for the detection of IgE-mediated reactions by exposing the mast cells of the skin to the suspected allergen in patients having experienced anaphylaxis.[8] The results of skin testing constitute the third component of the triad.

Why and When to Perform Skin Tests? Because premedication with H_1 and/or H_2 receptor antagonists and/or corticosteroid has not been proven to prevent anaphylaxis,[1,7,14] skin tests constitute the tool to (1) identify the culprit agent (and therefore to definitely

Fig. 2. The clinical pathway allows for the identification of the culprit agent, documenting the pathophysiologic mechanism (allergic *vs.* nonallergic) of the perioperative immediate reaction and allows for advice regarding subsequent anesthetics. NMBA = neuromuscular blocking agent.
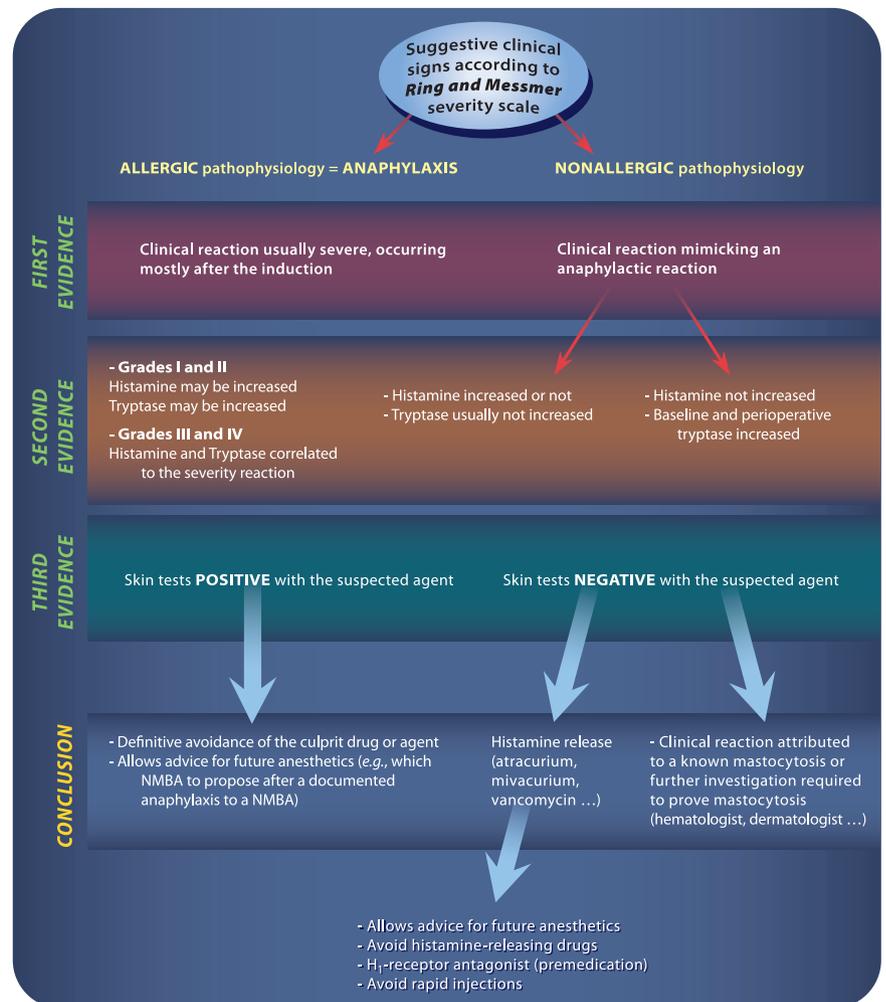
avoid it), (2) prove the pathophysiologic mechanism of the reaction (allergic *vs.* nonallergic), and (3) suggest a safe alternative drug for future exposures (fig. 2). A 4- to 6-week delay after the reaction is required to avoid a false-negative test result because of mast cell depletion.[1,7]

How to Perform Skin Tests? Skin testing should always be performed according to the clinical history to provide a pertinent diagnosis. Therefore, all drugs injected just before the reaction, as well as latex, must be skin tested, and immediate hypersensitivity reactions necessitate immediate reading of skin tests (*i.e.*, after 15–20 min). Before test agents, the cutaneous reactivity should be assessed with a negative (saline) and a positive control (codeine and/or histamine). Investigation of drugs is performed by prick tests (PTs), followed by intradermal tests (IDTs) using freshly prepared commercial solutions, diluted or undiluted, without exceeding the maximal concentrations to avoid false-positive results (table 2).[1,2,7,20] IDTs are more sensitive but less specific than PTs.[21] However, IDTs are more likely to trigger systemic allergic reactions and thus should be only performed after PTs.[21] Therefore, if the PT result is negative, the IDT is performed by injecting 0.02–0.05 ml

of the corresponding drug. If the IDT is negative, 10-fold increasing concentrations are used with incremental 15- to 20-min intervals between each IDT until the test result is positive or the highest nonirritant concentration is achieved.[1,2,7,20] The criteria of PT/IDT positivity and the different concentrations of anesthetic drugs that are normally nonreactive have been strictly defined in France (table 2).[7] These rules have been recommended in Scandinavia[1] and adapted by others[20] (for extensive review, see Dewachter and Mouton-Faivre[8]).

Which Drugs and Substances Are Involved?

Neuromuscular Blocking Agents. Neuromuscular blocking agents are frequently involved during perioperative anaphylaxis at a range of 50–70% according to different reports in Europe,[2,7,10,11] whereas limited data are available in the United States. There has not been an epidemiologic study of the causative agents of perioperative anaphylaxis in the United States. Instead, data rely on reports to the US Food and Drug Administration, and because of a lack of standardized skin testing, overall incidences in the United States are unknown. All NMBAs may elicit anaphylaxis.[8,20] The sensitivity of skin tests for NMBAs in patients having experienced anaphylaxis after an

Table 2. Concentrations of Anesthetic Agents Normally Nonreactive during Skin Tests

Drug	Concentration, mg/ml	Prick Test		Intradermal Test	
		Dilution	Maximal Concentration, mg/ml	Dilution	Maximal Concentration, μg/ml
NMBAs					
Suxamethonium	50	1/5	10	1/500	100
Atracurium	10	1/10	1	1/1,000	10
Cisatracurium	2	Undiluted	2	1/100	20
Mivacurium	2	1/10	0.2	1/1,000	2
Pancuronium	2	Undiluted	2	1/10	200
Rocuronium	10	Undiluted	10	1/100	100
Vecuronium	4	Undiluted	4	1/10	400
Hypnotics					
Etomidate	2	Undiluted	2	1/10	200
Midazolam	5	Undiluted	5	1/10	500
Propofol	10	Undiluted	10	1/10	1,000
Thiopental	25	Undiluted	25	1/10	2,500
Opioids					
Alfentanil	0.5	Undiluted	0.5	1/10	50
Fentanyl	0.05	Undiluted	0.05	1/10	5
Morphine	10	1/10	1	1/1,000	10
Remifentanil	0.05	Undiluted	0.05	1/10	5
Sufentanil	0.005	Undiluted	0.005	1/10	0.5
Local anesthetics					
Bupivacaine	2.5	Undiluted	2.5	1/10	250
Lidocaine	10	Undiluted	10	1/10	1,000
Mepivacaine	10	Undiluted	10	1/10	1,000
Ropivacaine	2	Undiluted	2	1/10	200

NMBA = neuromuscular blocking agent.

From French Society of Anesthesiology and Intensive Care Medicine: Reducing the risk of anaphylaxis during anaesthesia: Abbreviated text. Ann Fr Anesth Reanim 2002; 21(suppl 1):7–23, © Elsevier Masson SAS; and Dewachter P, Mouton-Faivre C: What investigation after an anaphylactic reaction during anaesthesia? Curr Opin Anaesthesiol 2008; 21(3):363–8. Used with permission.[7,8]

NMBA injection is greater than 95%, and their reproducibility is excellent.[7,8] The maximal concentration recommended should not be exceeded (table 2). Cross-reactivity between NMBAs is common and approximates 60–70%.[1,12,19,20] Consequently, to be complete, investigation for cross-reactivity with the other commercialized NMBAs should be performed to identify safe alternative regimens (*i.e.*, negative skin-tested NMBAs) during the diagnostic approach of NMBA-induced anaphylaxis.[1,2,7] In France and as promoted by others, cross-reactivity is performed by PTs followed by IDTs, because PTs are less sensitive than IDTs.[1,7] Conversely, others recommend PTs only.[2] Indeed, an arbitrary contraindication to all NMBAs cannot be accepted as the rule in case of a documented anaphylaxis to a NMBA, because this places an unfavorable burden for the anesthetic options for the patient in the future.

Do Skin Tests Overestimate the Incidence of Anaphylaxis to Rocuronium? Of particular interest, reports have suggested an increased frequency of anaphylaxis with rocuronium in France and in Norway, leading the Norwegian Medicine Agency to publish an alert reserving its use for urgent intubations.§

§ http://www.legemiddelverket.no/templates/InterPage____16057.aspx. Accessed July 13, 2009.

Propenyl-ammonium groups may account for this increased allergenicity.[12] This trend was not observed in Australia or in the United States. Therefore, some authors called into question the accuracy of skin tests in the diagnosis of allergy to NMBAs, arguing that false-positive skin test results due to inappropriate dilutions of rocuronium used by either PTs or IDTs might explain the high incidence reported.[22,23] Dilution thresholds were debated in controls. Dhonneur considered that undiluted and diluted (1/100, 1/10) solutions of rocuronium may induce false-positive PT results,[23] whereas Levy recommended at least 100-fold dilution before skin testing (IDTs).[22] Others showed that PT results were always negative with rocuronium,[24] whereas nonreactive rocuronium dilutions for IDTs were considered to be either at 1/10,000[24] or 1/100.[25] However, when, as in these controls, the pretest probability is very low (absence of previous clinical history), predictive values of skin tests with NMBAs remain unknown, and skin test results are not predictive of outcome.[2,7,20] Biopsies of rocuronium wheals performed in these controls confirmed the absence of mast cell degranulation.[22,24] Consequently, the "positive" skin responses may be attributed to a direct effect of NMBAs on cutaneous vasculature.[22,24] In contrast to control patients, skin tests

with NMBAs performed in anaphylactic patients are highly reliable and detect drug-induced IgE cross-linking with corresponding release of inflammatory mediators.[12,20] Therefore, skin tests performed in control *versus* anaphylactic patients cannot and should not be compared.[26] Nevertheless, the apparent increased incidence of anaphylaxis to rocuronium might be due to (1) a reflection of usage and market share, (2) biased reporting of adverse effects of new drugs, (3) statistical issues, or (4) genotypic differences.[19] This question requires further epidemiologic data in order to be understood.[2,19]

Other Drugs and Substances Involved.

Latex. In Europe, investigation of latex is performed by PTs using commercial extracts.[1,2,7] Their sensitivity is excellent (75–90%).[2] No commercially available skin test reagent exists in the United States, where diagnosis relies on *in vitro* tests.[15,19] Latex gloves extracts are often used, but their amount of latex proteins is not standardized.[14]

Antibiotics. Anaphylaxis triggered by antibiotics involves primarily penicillins and cephalosporins (70%) which share the β-lactam ring.[20] It may occur at first exposure.[1,21] The European Network Drug Allergy interest group on drug hypersensitivity proposed the highest skin testing concentrations as follows for amoxicillin (20–25 mg/ml), ampicillin (20–25 mg/ml), and most cephalosporins (1–2 mg/ml). The specificity of skin testing with β-lactams is between 97% and 99%, whereas the sensitivity is around 50%.[8] Therefore, oral provocation tests in patients with suggestive clinical history and negative skin test results with β-lactams is recommended.[1,20,21] Cross-reactivity between penicillins and cephalosporins seems to be low (10%) and is attributed to the common β-lactam ring.[19] However, the allergenicity of the molecule is also determined by the side chains attached to the β-lactam ring. Therefore, first-generation cephalosporins and cefamandole share a similar structural side chain with penicillin and amoxicillin.[2] A recent meta-analysis suggested that patients allergic to penicillin or amoxicillin have a higher incidence of allergic reactions to first-generation cephalosporins and cefamandole but not to later-generation cephalosporins.[2] Anaphylaxis with vancomycin remains rare; IDTs with vancomycin should be performed below a concentration of 10 μg/ml.[20] Anaphylaxis with vancomycin should be distinguished from red man syndrome, a clinical entity resulting from nonspecific histamine release and observed when the drug is rapidly injected.[14,20]

Hypnotics. Anaphylaxis to thiopental or propofol is rarely reported, whereas anaphylaxis to etomidate and ketamine remains extremely rare.[1,2,19] Hypnotics may be skin tested according to the concentration limits provided in table 2.[1,7,20]

Opioids. Anaphylaxis to opioids is very rare.[1,2,19,20] Morphine induces histamine release; the maximal concentration recommended for skin testing should not be exceeded (table 2). PTs, followed by IDTs, if negative, are performed with phenylpiperidines (alfentanil, fentanyl, remifentanil, sufentanil) (table 2).[1,7,20] Cross-reactivity remains uncommon among phenylpiperidines.[19]

Local Anesthetics. Anaphylaxis to local anesthetics is very uncommon and has decreased in frequency because of the decreasing use of the ester group of local anesthetics. Most allergic reactions are due to the common metabolic product of the ester local anesthetic, para-amino benzoic acid.[1,2,7,20] This common allergenic determinant implies cross-reactivity among all local anesthetics belonging to the ester group. Allergic reactions to amide local anesthetics remain anecdotal. Ingredients included in local anesthetic solutions such as antioxidants or preservatives including metabisulfite or parabens (also metabolized to para-amino benzoic acid) may also elicit allergic or adverse reactions.[19,20] Finally, cross-reactivity among esters is common, whereas it is rarely seen in the amide group and is absent between esters and amides. Local anesthetics (without preservatives or epinephrine) may be skin tested according to the concentration limits provided in table 2.[1,7,20]

Colloids. Anaphylaxis with colloids is rare but is more frequent with gelatins (0.35%) than with hydroxyethylstarch (0.06%).[19] Skin tests may be performed with PTs (pure solution) followed by IDTs in case of negativity.[1,7,20]

Aprotinin. The risk of anaphylaxis with aprotinin is approximately 2.8% in reexposed patients.[20] Aprotinin was previously used to reduce blood loss and the need for blood transfusion during surgery, but it was recently withdrawn from the market. However, some fibrin glue products still contain aprotinin. PTs (pure solution) followed by IDTs (up to 1/10 dilution) in case of negativity are recommended.[7,20]

Dyes. The incidence of anaphylaxis to isosulfan or patent blue is less than 2%,[19] whereas methylene blue is very rarely involved. Dyes may be skin tested by PTs followed by IDTs (up to 1/100 for methylene blue because it is a histamine-releaser and up to 1/10 dilution for isosulfan/patent blue).[19]

Other Drugs. Protamine, antiseptics (chlorhexidine, povidone iodine), and iodinated contrast agents may also induce anaphylaxis. Skin testing may be performed to prove the diagnosis.[1,19]

Finally, to ensure an accurate diagnosis and to provide subsequent recommendations for future anesthetic management, the interpretation of the allergologic assessment should always be linked to the clinical event. A suggestive clinical history (most severe reaction) associated with an increased tryptase concentration (absence of tryptase increase does not preclude the diagnosis)[1,2,7] linked to skin tests positivity to the suspected agent confirm the diagnosis of anaphylaxis to this agent, which should be avoided.

Conversely, a suggestive clinical history (in general not a severe reaction) associated with an increase (or not) of histamine without a tryptase increase along with skin test negativity suggests a nonallergic reaction (histamine

release with potent histamine-releasing drugs such as atracurium, mivacurium, and vancomycin).

Furthermore, a suggestive clinical history (essentially severe disturbances of cardiovascular homeostasis) associated with a tryptase increase and a persistent increased baseline tryptase along with skin test negativity suggests mastocytosis[8] (fig. 2).

Most importantly, patients should be given a detailed report with unequivocal answers to provide to caregivers before future anesthetic exposures.

Risk Factors for Perioperative Anaphylaxis

Ideally, all patients experiencing an episode of perioperative anaphylaxis would have undergone an allergologic assessment before further anesthetics. The reality is very different. In many countries, the allergologic assessment is not routinely performed. Identification of at-risk patients is therefore required before any procedure requiring anesthetics which must be conducted in a manner to avoid a suspected drug or agent. Patients who have had previous uninvestigated severe immediate reactions during anesthesia are at increased risk of a recurrence during subsequent anesthetics.[1,2,7] Regional anesthesia is preferred whenever possible.[1,7] Moreover, a latex-free environment should be used to prevent a perioperative clinical reaction in patients having experienced clinical manifestations of allergy when exposed to latex, in patients who had many surgical or urologic cannulation procedures (because of the high incidence of sensitization to latex), and in patients with clinical manifestations of allergy to tropical fruits (*e.g.*, avocado, banana, kiwi, pineapple, papaya) because of the high rate of cross-reactivity with latex (also called *latex-fruit syndrome*).[7] In contrast, patients who are atopic (except for latex) or those who are allergic to a drug (except for antibiotics which may be injected as perioperative antibiotic prophylaxis) that is not likely to be used during the perioperative period are not considered to be at risk for perioperative anaphylaxis.[7]

Treatment of Perioperative Anaphylaxis

The following measures should be applied whenever possible: (1) withdraw the suspected culprit drug; (2) immediately discontinue anesthetic drugs when the anaphylactic event occurs during induction; (3) maintain the airway with 100% oxygen; (4) provide early administration of epinephrine in case of grade III or IV reactions; (5) call for help, especially for grade III and IV reactions; (6) place the patient supine in the Trendelenburg position; and (7) abbreviate the surgical procedure if possible when it occurs during surgery.

Restoration of the Cardiovascular Homeostasis Is First Priority

Administration of intravenous epinephrine and an expansion of intravascular volume are the key points of perioperative management of anaphylaxis.[1,2,7,27] There is no absolute contraindication during anaphylaxis for the use of epinephrine when the clinical situation dictates its use,[14] and early administration should be the rule.[1,2,7,27] Therefore, poor outcomes during anaphylaxis, including deaths, are associated with either late or absent administration of epinephrine or inadequate or excessive dosing, emphasizing the need for careful titration.[1]

Epinephrine should never be injected during grade I reactions, whereas titrated boluses (10–20 μg) of epinephrine may be sometimes necessary during grade II (table 1). Conversely, titrated intravenous bolus administrations of epinephrine (100–200 μg) are required in grade III reactions, renewed every 1 or 2 min if necessary according to the hemodynamic response and followed by a continuous infusion (1–4 μg/min) to prevent the need for repeated bolus injections.[1,2,7,27] Grade IV reactions (cardiac arrest) require cardiopulmonary resuscitation and high doses of epinephrine.[7,27] A commonly used sequence is to administer 1–3 mg intravenously (over 3 min) and 3–5 mg intravenously (over 3 min) followed by a continuous infusion (4–10 μg/min).[27]

Fluid Therapy

Changes in vascular permeability during anaphylaxis might permit, within 10 min, a 50% transfer of the intravascular fluid into the interstitial space.[14] Fluid therapy initiated with either crystalloids or colloids is therefore essential to compensate for large fluid shifts and should be initiated early.[1,2,7,27]

Bronchospasm

Bronchospasm is treated with inhaled β_2 agonist (salbutamol or albuterol).[1,2,7,27] In cases of persistent bronchospasm, intravenous injection of a β_2 agonist (salbutamol, 100–200 μg) is recommended, and a continuous infusion (5–25 μg/min) should be considered.[2,7,27] In contrast, when cardiovascular collapse and bronchospasm occur together, epinephrine remains the first-line therapy to correct first the cardiovascular homeostasis disturbances, whereas its β_2 effect is effective in relieving bronchoconstriction.[7,27] Intravenous corticosteroids early in the course of therapy are recommended because of their antiinflammatory effects. Their beneficial effects are delayed at least 4–6 h.[1,7,27]

Additional Therapy

Corticosteroids and/or H_1 receptor antagonists are often recommended in the management of anaphylaxis,[1,2,7,27] but their effects have never been evaluated in placebo-

controlled trials.[14] In retrospective studies analyzing recurrent episodes of anaphylaxis, corticosteroids and antihistamines did not prevent biphasic anaphylaxis, indicating that patients should be followed up carefully after apparent remission of anaphylaxis. However, corticoids are useful for angioedema.[1]

Anaphylactic Shock Refractory to Catecholamines: Alternative Therapy?

Epinephrine sometimes fails to restore the profound disturbances of cardiovascular homeostasis. This singular clinical entity is called *anaphylactic shock refractory to catecholamines*, although it remains undefined in the literature. Norepinephrine, metaraminol, or glucagon for patients receiving β-blocker therapy is recommended in this clinical setting.[1,2,7] Because desensitization of adrenergic receptors might be one of the contributing factors of catecholamine failure occurring during anaphylaxis, arginine vasopressin (AVP) may be an alternative through its vasoconstrictive effects mediated by nonadrenergic vascular AVP V_1 receptors. Another factor contributing to catecholamine failure may involve nitric oxide (which seems to play a pivotal role during anaphylaxis) because increased nitric oxide synthesis contributes to the hypotension and resistance to vasopressors during vasodilatory shock. Thus, AVP directly decreases intracellular concentrations of the nitric oxide second messenger, guanosine 3′,5′-cyclic monophosphate.[28] Although experimental work provides support for the possible use of AVP during anaphylaxis,[28] AVP may be detrimental when injected alone in the early course of anaphylaxis (5 min)[28] or when higher doses are used. However, several case reports suggest that AVP might be considered as a potential rescue therapy during anaphylaxis. Therefore, some patients experiencing anaphylaxis refractory to epinephrine, norepinephrine, and/or phenylephrine were successfully treated with AVP injected at least 10–20 min after shock onset.[29] AVP could therefore play a pivotal role in cases of catecholamine failure occurring during anaphylaxis. Nevertheless, it is important that both successful and unsuccessful uses of AVP during resuscitation attempts during anaphylaxis be reported, such that a fair assessment of its potential usefulness can be established.

Moreover, methylene blue is known to interfere with nitric oxide–mediated vascular smooth muscle relaxation and was recently successfully used in catecholamine- and vasopressin-resistant anaphylaxis.[30] Finally, preclinical studies are needed to better understand the mechanism and potential clinical value of these rescue therapies.

Conclusion and Perspectives

Perioperative anaphylaxis is a severe and rapid clinical condition that can be lethal even in previously healthy patients. The diagnosis of perioperative anaphylaxis might be missed because the clinical presentation of this infrequent pathology can be of very rapid onset with variable clinical signs. Optimal management of perioperative anaphylaxis should therefore be encouraged through teaching applications such as an anesthesia simulator to compensate for the low frequency with which the average practitioner would encounter anaphylaxis in routine clinical care. Ideally, the combination of clinical, biochemical, and skin test evidence will identify the culprit agent and will allow the informed practitioner to avoid these agents in future clinical procedures. Moreover, the failure of catecholamines to restore cardiovascular homeostasis during anaphylaxis should receive more attention, especially regarding the establishment of precise recommendations about the potential indications of AVP in this clinical setting.

References

1. Kroigaard M, Garvey LH, Gillberg L, Johansson SG, Mosbech H, Florvaag E, Harboe T, Eriksson LI, Dahlgren G, Seeman-Lodding H, Takala R, Wattwil M, Hirlekar G, Dahlen B, Guttormsen AB: Scandinavian Clinical Practice Guidelines on the diagnosis, management and follow-up of anaphylaxis during anaesthesia. Acta Anaesthesiol Scand 2007; 51:655–70
2. Harper NJ, Dixon T, Dugue P, Edgar DM, Fay A, Gooi HC, Herriot R, Hopkins P, Hunter JM, Mirakian R, Pumphrey RS, Seneviratne SL, Walls AF, Williams P, Wildsmith JA, Wood P, Nasser AS, Powell RK, Mirakhur R, Soar J: Suspected anaphylactic reactions associated with anaesthesia. Anaesthesia 2009; 64:199–211
3. Johansson SG, Hourihane JO, Bousquet J, Bruijnzeel-Koomen C, Dreborg S, Haahtela T, Kowalski ML, Mygind N, Ring J, van Cauwenberge P, van Hage-Hamsten M, Wuthrich B: A revised nomenclature for allergy: An EAACI position statement from the EAACI Nomenclature Task Force. Allergy 2001; 56:813–24
4. Sampson HA, Munoz-Furlong A, Campbell RL, Adkinson NF Jr, Bock SA, Branum A, Brown SG, Camargo CA Jr, Cydulka R, Galli SJ, Gidudu J, Gruchalla RS, Harlor AD Jr, Hepner DL, Lewis LM, Lieberman PL, Metcalfe DD, O'Connor R, Muraro A, Rudman A, Schmitt C, Scherrer D, Simons FE, Thomas S, Wood JP, Decker WW: Second symposium on the definition and management of anaphylaxis: Summary Report-Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network symposium. J Allergy Clin Immunol 2006; 117:391–7
5. Evora PRB, Simon MR: Role of nitric oxide production in anaphylaxis and its relevance for the treatment of anaphylactic hypotension with methylene blue. Ann Allergy Asthma Immunol 2007; 99:306–13
6. Ring J, Messmer K: Incidence and severity of anaphylactoid reactions to colloid volume substitutes. Lancet 1977; 1:466–9
7. French Society of Anesthesiology and Intensive Care Medicine: Reducing the risk of anaphylaxis during anaesthesia: Abbreviated text. Ann Fr Anesth Reanim 2002; 21(suppl 1):7–23
8. Dewachter P, Mouton-Faivre C: What investigation after an anaphylactic reaction during anaesthesia? Curr Opin Anaesthesiol 2008; 21:363–8
9. Lienhart A, Auroy Y, Pequignot F, Benhamou D, Warszawski J, Bovet M, Jougla E: Survey of anesthesia-related mortality in France. ANESTHESIOLOGY 2006; 105:1087–97
10. Harboe T, Guttormsen AB, Irgens A, Dybendal T, Florvaag E: Anaphylaxis during anesthesia in Norway: A 6-year single-center follow-up study. ANESTHESIOLOGY 2005; 102:897–903
11. Lobera T, Audicana MT, Pozo MD, Blasco A, Fernández E, Cañada P, Gastaminza G, Martinez-Albelda I, González-Mahave I, Muñoz D: Study of hypersensitivity reactions and anaphylaxis during anesthesia in Spain. J Investig Allergol Clin Immunol 2008; 18:350–6
12. Baldo BA, Fisher MM, Pham NH: On the origin and specificity of antibodies to neuromuscular blocking (muscle relaxant) drugs: An immunochemical perspective. Clin Exp Allergy 2009; 39:325–44
13. Kounis NG: Kounis syndrome (allergic angina and allergic myocardial infarction): A natural paradigm? Int J Cardiol 2006; 110:7–14
14. Practice Parameters of the Joint Task Force on Practice Parameters for Allergy and Immunology: The diagnosis and management of anaphylaxis—An updated practice parameter. J Allergy Clin Immunol 2005; 115:S483–523
15. Hepner DL, Castells MC: Latex allergy: An update. Anesth Analg 2003; 96:1219–29

16. Turillazzi E, Greco P, Neri M, Pomara C, Riezzo I, Fineschi V: Anaphylactic latex reaction during anaesthesia: The silent culprit in a fatal case. Forensic Sci Int 2008; 179:e5–8

17. De Queiroz M, Combet S, Berard J, Pouyau A, Genest H, Mouriquand P, Chassard D: Latex allergy in children: Modalities and prevention. Paediatr Anaesth 2009; 19:313–9

18. Brown RH, Hamilton RG, Mintz M, Jedlicka AE, Scott AL, Kleeberger SR: Genetic predisposition to latex allergy: Role of interleukin 13 and interleukin 18. ANESTHESIOLOGY 2005; 102:496–502

19. Hepner DL, Castells MC: Anaphylaxis during the perioperative period. Anesth Analg 2003; 97:1381–95

20. Ebo DG, Fisher MM, Hagendorens MM, Bridts CH, Stevens WJ: Anaphylaxis during anaesthesia: Diagnostic approach. Allergy 2007; 62:471–7

21. Mirakian R, Ewan PW, Durham SR, Youlten LJ, Dugue P, Friedmann PS, English JS, Huber PA, Nasser SM: BSACI guidelines for the management of drug allergy. Clin Exp Allergy 2009; 39:43–61

22. Levy J, Gottge M, Szlam F, Zaffer R, McCall C: Weal and flare responses to intradermal rocuronium and cisatracurium in humans. Br J Anaesth 2000; 85: 844–9

23. Dhonneur G, Combes X, Chassard D, Merle JC: Skin sensitivity to rocuronium and vecuronium: A randomized controlled prick-testing study in healthy volunteers. Anesth Analg 2004; 98:986–9

24. Berg CM, Heier T, Wilhelmsen V, Florvaag E: Rocuronium and cisatracurium-positive skin tests in non-allergic volunteers: Determination of drug concentration thresholds using a dilution titration technique. Acta Anaesthesiol Scand 2003; 47:576–82

25. Mertes PM, Monneret-Vautrin DA, Leynadier F, Laxenaire MC: Skin reactions to intradermal neuromuscular blocking agent injections: A randomized multicenter trial in healthy volunteers. ANESTHESIOLOGY 2007; 107:245–52

26. Dewachter P, Mouton-Faivre C: Skin testing performed in individuals cannot be compared with responses from anaphylactic patients. Anesth Analg 2008; 107:1441

27. American Heart Association: Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care, part 10.6: Anaphylaxis. Circulation 2005; 112:IV143–5

28. Dewachter P, Raeth-Fries I, Jouan-Hureaux V, Menu P, Vigneron C, Longrois D, Mertes PM: A comparison of epinephrine only, arginine vasopressin only, and epinephrine followed by arginine vasopressin on the survival rate in a rat model of anaphylactic shock. ANESTHESIOLOGY 2007; 106:977–83

29. Schummer C, Wirsing M, Schummer W: The pivotal role of vasopressin in refractory anaphylactic shock. Anesth Analg 2008; 107:620–4

30. Del Duca D, Sheth SS, Clarke AE, Lachapelle KJ, Ergina PL: Use of methylene blue for catecholamine-refractory vasoplegia from protamine and aprotinin. Ann Thorac Surg 2008; 87:640–2