Anesthesia and anaphylaxis

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SUMMARY

Allergic reaction during anesthesia happens more often than expected. The main problem is the unawareness of the patient regarding this condition. The aim of this paper is to provide the definition of anaphylaxis, review the immunopathogenic mechanisms of the allergic reactions that anesthesiologists most commonly face and provide a guidance to manage a patient with a suspected anaphylaxis reaction. The clear understanding of the cellular physiopathology, of the consequences of the activation of the cellular membranes, mastocytes, basophiles, and of the pharmacology of the mediators such as histamine, protease and lipids is essential. The knowledge and quick identification of the agents that most frequently cause an anaphylactic reaction, such as muscle relaxants, latex, antibiotics, hypnotics, etc., is key to prevent and treat anaphylactic reactions in programmed anesthesia and in emergencies.

Key words: Anaphylaxis, hypersensitivity, Prick test, atopic, anesthesia.

RESUMEN

Las reacciones de hipersensibilidad en anestesiología se presentan con una frecuencia mayor a la esperada. El problema principal es que el paciente desconoce este antecedente. El propósito de la presente revisión es exponer la definición de anafilaxia, los mecanismos immunopatológicos involucrados en las reacciones de hipersensibilidad a las que se enfrentan frecuentemente los anestesiólogos; así como proponer un plan de tratamiento y abordaje en un paciente con sospecha de una reacción anafiláctica. La comprensión de la fisiopatología celular, de la activación de las membranas celulares, de las consecuencias de la activación de membranas de los mastocitos y basófilos, de la farmacología de los mediadores como la histamina, proteasas y mediadores lipídicos es de vital importancia. El reconocimiento de los agentes causales más comunes de reacciones anafilácticas como los relajantes musculares, látex, antibióticos, hipnóticos, etc., son parte fundamental de la prevención y tratamiento de las reacciones anafilácticas en anestesia programada o de urgencias.

Palabras clave: Anafilaxia, reacción anafilactoide, hipersensibilidad, intradermorreacciones (prick tests), atopia, anestesia.
INTRODUCTION

Portier and Richet proposed the term anaphylaxis in 1902(1) to define a potentially lethal adverse systemic reaction that affects more than two organs or systems after a person has been exposed to a foreign agent. Despite that the first case was reported more than one-hundred years ago, both the definition and treatment of this condition remain controversial(2).

The diagnosis of anaphylaxis when the patient is anesthetized is difficult. Its incidence varies from 1:3,500 to 1:20,000 and most anesthesiologists have no experience with cases of anaphylaxis(3). The skin manifestations are difficult to identify in early stages because drapes cover the patient during the surgical procedure, respiratory signs are minimized due to the bronchodilator effect of the inhaled anesthetic drugs, and pharmacological hypotension is common; therefore, diagnosis and initial treatment with adrenaline are often delayed. Anesthesiologists should be familiarized with early clinical manifestations, physiopathology and treatment of this condition.

DEFINITION

Anaphylaxis is a systemic syndrome of immediate hypersensitivity (Type I, according to the classification of Gell and Coombs) that is caused by the IgE mediated release of preformed mediators of mastocytes and basophiles. Its clinical manifestations are bronchospasm, angioedema, rash and, in its most severe form, cardiovascular collapse(4). Anaphylactoid reactions are clinically indistinguishable from anaphylaxis, but are not IgE mediated.

PHYSIOPATHOLOGY AND CHEMICAL MEDIATORS OF ANAPHYLAXIS

The Gell-Coombs classification differentiates four types of hypersensitivity reactions: Type I: immediate (IgE dependent); Type II: cytotoxic (IgM and IgE dependent); Type III: immune complexes; Type IV: delayed (T-lymphocytes dependent)(5). Besides the IgE mediated reactions, cytotoxic mechanisms (transfusion reactions) and immune complexes (gamma-globulin immune complexes administered intramuscularly or intravenously) are involved as well. Table I lists the possible factors that trigger anaphylaxis and these are classified according to the responsible immunopathological mechanism(6).

Anaphylactic reactions occur after the release of biochemical mediators and chemotactic substances during the degranulation of basophiles and mastocytes. The mediators (histamine, tryptase, heparin, chymase, and cytokines) are preformed substances stored in the granules of these cells; also, they originate from the synthesis of lipid-derived molecules (prostaglandins, leukotrienes, platelet-activating factors)(7).

Type I or IgE mediated hypersensitivity requires a sensitization process, which involves an individual’s exposure to a foreign substance, known as antigen or allergen and as a consequence, the formation of an IgE specific antibody against the allergen; at this moment there are no clinical manifestations. IgE antibodies bind to the high affinity IgE receptor (FcERI) on the surface of mastocytes and basophiles. After the second contact, the allergen binds to the IgE specific receptor on the surface of the above mentioned cells. This event triggers a signal, which in turns activates the membrane, thereby causing the synthesis and release of mediators.

During the anaphylactoid reactions, there is an activation of cell membranes that is not mediated by antibodies; consequently, the release of histamine is not specific. The main characteristic is that previous contact with the substance that triggers the reaction is not necessary, thus, it can occur with the first exposure and in general no mediators are synthesized. The drugs involved in anaphylaxis are basic compounds that cause a reaction in a receptor to the polycyclicamines that are on the mastocytes surface. The release of mediators depends upon the dose and osmolarity of the substance(8,9).

The intensity of the clinical manifestations is variable and depends on the drug associations and the speed of the injection: rapid intravenous administration of many histamine-releasers agents can cause a massive release of histamine.

Table I. Immunopathological mechanisms.

<table>
<thead>
<tr>
<th>Type I</th>
<th>Type II</th>
<th>Type III</th>
<th>Type IV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anaphylactic (IgE dependent): foods, medications, poison, latex, allergies to vaccines, hormones, animal and vegetables proteins, dyestuff, enzymes, polysaccharide, exercise (possibly in events dependent upon meals or drugs)</td>
<td>Contrast media used in radiology, ACE inhibitors administered during the dialysis procedures with cuprophone, or polymethyl-methacylate dialysis membranes; ethylene oxide gas in the dialysis system, protamine (probably)</td>
<td>Immune aggregates: intravenous immunoglobulin, dextran (probably), in Asian subjects, anti haptoglobin, haptoglobinemia</td>
<td>Cytotoxicity: transfusion reactions to cellular elements</td>
</tr>
<tr>
<td>Anaphylactoid (IgE non-dependent): contrast media used in radiology, ACE inhibitors administered during the dialysis procedures with cuprophone, or polymethyl-methacylate dialysis membranes; ethylene oxide gas in the dialysis system, protamine (probably)</td>
<td>Non-specific degranulation of mastocytes and basophiles: opioids, muscle relaxants, idiopathic, physical factors (exercise, cold, heat)</td>
<td>Immune aggregates: intravenous immunoglobulin, dextran (probably), in Asian subjects, anti haptoglobin, haptoglobinemia</td>
<td>Psychogenic: Ficticia, somatomorphic undifferentiated idiopathic anaphylaxis</td>
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mine, which is associated with severe clinical signs. This mechanism can be observed with different types of medications that are used in anesthesia (hypnotics, morphinics, and muscle relaxants) and with contrast media used in radiology. Given that this is an unspecific reaction, a subsequent injection of the same medication may not produce a new reaction. This is different from the immunological phenomenon.

Another way of activating the cell membranes is through activating the complement cascade. The complement system is a set of proteins that are activated in sequence after the fixation of the antigen-antibody complex (IgG and IgM are immunoglobulines able to fix to the complement), which is the classic activation pathway, or through the contact of certain molecular structures (polysaccharides, polyanions, bacterial endotoxins), which is the alternate pathway. During activation of the complement, two degradation proteins are formed, C3a and C5a, which are called anaphylotoxins. These are capable of releasing histamine from basophiles and mastocytes, cause smooth muscle contraction and increase capillary permeability.

The membrane of the mastocytes has the receptors for the anaphylotoxins. Stimulating these receptors is one of the more potent membrane activators. This mechanism could be the cause of reactions to dextran and protamine.

Consequences of the membrane activation and its regulation

Activation of cell membrane, regardless of the mechanisms, causes both degranulation with the release of stored mediators, and synthesis of mediators.

During anaphylaxis, the binding of two IgE molecules fixated to the mastocytes membrane triggers the activation of adenyl cincle, which in turn synthesizes cyclic adenosine monophosphate (cAMP); in a parallel way, the rate of intracellular calcium increases due to the opening of the calcium channels. The increase in of cAMP causes the activation of protein kinases, which in turn prompt phosphorylation of cytoplasmic proteins. This promotes the formation of microtubules, which will allow the movement of the preformed granules through the cell membrane. The flow of calcium activates phospholipase A2, which induces the release of arachidonic acid to destroy membrane phospholipids. The arachidonic acid is metabolized into prostaglandins, which are neoformed vasoactive substances, through the cyclooxygenase pathway, and leukotrienes, through the lipoxygenase pathway. At the nuclear level, the genes that codify certain cytokines for the delayed synthesis of the tumoral necrosis factor (TNF) and interleukins that perpetuate the inflammatory reaction are activated.

PHARMACOLOGY OF ALLERGIC MEDIATORS

The mediators responsible for allergic reactions are:

- Preformed mediators: histamine, proteases, tryptase, chymase, heparin, histamine releasing factor and other cytokines.
- Neoformed lipidic mediators: leukotrienes, prostaglandins, platelet-activating factor.

A description of the pharmacologic action of these mediators helps to understand several clinical aspects of hypersensitive reactions(11).

- **Histamine**

This is the main molecule released in allergic reactions, which causes most symptoms. Perfusion of histamine in volunteers induces reactions similar to those observed in allergic reactions: erythema, tachycardia, and headache; in higher doses, histamine causes hypotension and a decrease in systemic arterial resistance.

Histamine has an effect on H1 and H2 receptors in the target organs of allergic reactions: skin, respiratory airways, myocardium, vascular walls, and the digestive tract. Activation of H1 receptors causes pruritus, rhinorrhea, tachycardia and bronchospasm, whereas both H1 and H2 receptors are responsible for headache, rubor and hypotension(12). The histamine levels correlate with the persistence of cardiopulmonary symptoms. Histamine exerts its effects by binding to H1 receptors stimulating endothelial cells to convert L-arginin into nitric oxide (NO), which is a potent vasodilator and furthermore decreases venous return. However, trying to use NO inhibitors during anaphylaxis causes bronchospasm and coronary vasoconstriction, suggesting that NO plays a regulatory role in the symptoms of anaphylaxis but exacerbates the associated vasodilatation(13).

- **Proteases**

Tryptase is the main protease that is released when the process of mastocyte degranulation occurs. The serum tryptase is specific for degranulation and measuring its level allows for ascertaining the origin of anaphylactic shock. Its physiology is not well known. Tryptase participates in the catabolism of the third component (C3) of the complement.

- **Lipidic mediators**

- Leukotrienes: lipoxygenase transforms the arachidonic acid of cell membranes into 5-hydroxyeicosatetraenoic acid (5-HETE) and leukotrienes: LTB4 (chemotactic ac-
CAUSES OF ANAPHYLACTIC ACCIDENTS

Severe anaphylaxis affects 1-3 per 10,000 people in the world, although it is more common in the United States of America and Australia. It has been estimated as cause of death in 0.65% to 2% of patients. During anesthetic procedures, the incidence of severe anaphylaxis varies from 1:3,500 to 1:20,000. Mortality due to anesthesia is as high as 6% and the ratio of women to men is 4:1, signifying that gender is important. This pattern is more evident when muscle relaxants are used, whereby the ratio increases to 8 women per 1 man.

Patient’s anxiety during preanesthesia is identified as a significant risk factor in most studies since anxiety favors the release of histamine. Furthermore, some individuals release histamine more easily, such as those with dermatographism, sun allergies or erythema caused by histamine releasing foods (strawberries, seafood, and wine). This release of non-specific histamine is explored through skin tests with substances such as codeine.

The frequency of atopy (asthma, allergic rhinitis, eczema) in individuals that have suffered anaphylaxis due to exposure to an anesthetic is more common than in the general population(16).

A true drug allergy is a well-known risk factor for anaphylaxis. Its frequency is significantly more increased in those who have had an accident due to exposure to an anesthetic, relative to the general population. The risk related to penicillin exposure is among the most analyzed. Currently, parenteral antibiotics are considered to be responsible for up to 15% of anaphylactic episodes that occur during the anesthetic procedure; they occupy third place after muscle relaxants and latex(17). Muscle relaxants are the main cause of anaphylaxis (58.2%) and rocuronium is most commonly involved. Succinylcholine is responsible for at least 50% of anaphylactic shock episodes, despite its decreased use over the last years.

Most anaphylactic shock episodes due to muscle relaxants are truly IgE mediated anaphylaxis type, although, some of these drugs release histamine (succinylcholine, atracurium) and they can induce an anaphylactoid shock. Some muscle relaxants share a tertiary or quaternary ammonium group. If a patient already had a reaction to a muscle relaxant, then a cross-reaction to other muscle relaxant can occur; this is one of the peculiarities related to sensitization to this group of drugs (Table II).

Specific risk factors have been identified as being related to anaphylactic shock and muscle relaxants: occupational exposure to quaternary ammonium (health care professionals, paramedics, hair stylists); and the association of atopy with a history of allergy. With allergies to latex, it is more common to find atopy, occupational exposure, particular food allergies (banana, avocado, pecan) and repetitive contact with the allergen (children suffering spina bifida managed with intermittent catheterization)(18).

Opioids are responsible for 2.5% of anesthesia accidents and this figure is constant among different studies.

CLINICAL CHARACTERISTICS OF ANAPHYLAXIS

The signs and symptoms of anaphylaxis can manifest within a span of a few seconds to hours after exposure to the allergen. Most reactions occur within the first hour; in general, if the appearance of the symptoms takes longer, the reaction tends to be less severe. One third of children with severe anaphylaxis will have a biphasic reaction(19). In such cases, the patients will develop classic symptoms of anaphylaxis, they seem to recover and become asymptomatic until a second wave of symptoms occurs, which can be more severe than the initial one.

### Table II. Responsible drugs for anaphylactic accidents (in order of frequency).

<table>
<thead>
<tr>
<th>Position</th>
<th>Drug</th>
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<tbody>
<tr>
<td>1</td>
<td>Muscle relaxants</td>
</tr>
<tr>
<td>2</td>
<td>Latex</td>
</tr>
<tr>
<td>3</td>
<td>Antibiotics, particularly beta-lactams</td>
</tr>
<tr>
<td>4</td>
<td>Hypnotic agents or inducers</td>
</tr>
<tr>
<td>5</td>
<td>Opioids</td>
</tr>
<tr>
<td>6</td>
<td>Colloids, particularly dextran and mannitol</td>
</tr>
<tr>
<td>7</td>
<td>Blood products</td>
</tr>
<tr>
<td>8</td>
<td>Others such as: protamine, hemostatic gel, ethylene oxide, chemopapain, methyl methacrylate</td>
</tr>
</tbody>
</table>
but symptoms can return at a later time. Bronchospasm is severe and sometimes is refractory to the treatment with beta-antagonists and it can cause severe hypoxia. Fatal reactions have been reported after early discharge as a result of a biphasic reaction.

The chief clinical characteristic of cardiovascular involvement during anaphylaxis is hypotension, which is due to vasodilatation and capillary fluid leakage. This results in a mixed distributive-hypovolemic shock pattern. The intravascular fluid can decrease up to 35% in the first ten minutes. Poor cardiac output is due to the poor venous return and to the myocardial ischemia, in which hypoxia participates. The elevated levels of catecholamines (therapeutic and/or endogenously released) can have an adverse effect on the heart(20).

Table III lists the signs and symptoms of anaphylaxis in relation to the systems and organs involved.

### TREATMENT

The clinician must recognize the symptoms and signs of anaphylaxis early during care. The AAAAAI and the ACAAI proposed an algorithm(22) that includes:

1. Reanimation (A,B,C, level of consciousness)
2. Administer epinephrine intravenously: aqueous epinephrine 1:1000 (1 mg/1 mL), 0.2 to 0.5 mL (0.01 mg/kg in children, maximum dose: 0.3 mg) intramuscular every 5 minutes as needed to control symptoms and increase blood pressure. Injection in the vastus lateralis results in faster absorption rates and better plasma levels in both children and adults.

3. Once the IV line is accessible, begin the reanimation procedure with volume.

4. If hypotension persists, consider the following sequence:
   a) IV infusion of epinephrine using an infusion pump,
   b) Intravenous bolus of atropine if there is significant bradycardia,
   c) Intravenous bolus of a vasoconstrictor (methoxamine, vasopresine),
   d) Invasive monitorization,
   e) Intravenous glucagon, milrinone, amrinone or mechanical support (intra-aortic balloon counterpulsation).

#### Adjutant therapy

Other drugs are indicated as part of the support therapy, according to the clinical manifestations and the systems and organs involved in anaphylaxis(23):

1. Methylprednisolone (bronchospasm) 125 mg IV every 6 hours, adult dose or 1.2 mg/kg/day in children.
2. Diphenhydramine (skin rash) 1-2 mg/kg for children or 25-50 mg administered via parenteral.
3. Salbutamole (bronchospasm) nebulization with 0.5 ml of 0.5% solution diluted in 2.5 mL of isotonic saline solution or 2 inhalations of a metered dose inhaler (MDI) every 15 minutes until completing three dosages.
4. Ranitidine: 50 mg adult dose or 1 mg/kg/dose to infuse in 10-15 minutes.
5. Intravenous fluids: 1 lt of isotonic saline solution every 20-30 minutes according to the need to maintain adequate blood pressure, or 20 mL/kg/dose in children.
6. Infusion of epinephrine: 1:10,000 solution, 1 \( \mu \)g/min to 10 \( \mu \)g/min.

Patients that are taking beta-blockers are at risk of developing severe manifestations, such as paradoxical bradycardia, profound hypotension and severe bronchospasm. Beta-blockers can hamper the effectiveness of the treatment with epinephrine. To avert the blockage of beta receptors, escalating doses (up to 80 times) of isoproterenol (a nonselective beta adrenergic agonist) are needed experimentally(24).

### PREVENTION OF ANAPHILAXIS ACCIDENTS

Taking preventive measures should begin at the preanesthetic visit. During the consultation the following should be done:

1. To identify the subjects at risk
2. To organize an allergological profile
3. To define the pre-anesthetic drugs
4. To outline the anesthetic plan
Identifying the subjects at risk

The subjects at risk are identified according to the risk factors that were described previously. In a schematic way, there are four types of patients:

- Healthy subject without any risk factor
- Moderate risk subjects: an individual with anxiety, history of atopy (asthma, rhinitis, eczema), history of true drug allergy. If the subject exhibits the latter, it is advisable to use preanesthetic drugs and to delineate an anesthetic plan that reduces the risk of histamine release.
- High risk subjects: Patients that have a history of allergic reactions in which general anesthetic was used. Consulting the previous medical chart to see which drugs were used, etc. is advisable. In these patients it is imperative to use diagnostic tests to search for the allergen responsible for previous reactions.
- Patients that are under treatment with beta-blockers\(^{25}\).

Allergological profile

The clinical history should be precise, if possible, about the nature of the accident and drugs that were used. This profile comprises two types of tests:

- **In vivo** tests: skin tests and intradermic tests
- **In vitro** tests: quantification of IgE with ImmunoCap technique (Capsystem FEIA), leukocyte histamine release test (LHRT) and human mastocytes degranulation test.

**Skin prick test**

This test is needed to activate the dermal mastocytes membrane in order to release dermal histamine. This is activated, either in a non-specific way by “histamine-release” substances, or in a specific way by the intermediary of the bridge between two allergen-specific IgE molecules and fixated in the mastocytes membrane. The latter mechanism assumes a previous encounter with the allergen that results in sensitization.

Most drugs act as monovalent haptens, incapable of forming a bridge between two IgE molecules. Only the muscle relaxants are spontaneously divalent. For other drugs, the bridge is more random; it is formed through the plasma proteins fixation or the molecule polymerization. There is experience in tests with muscle relaxants in different dilutions, latex and antibiotics\(^{26,27}\).

**Skin tests**

The skin tests are easy to perform, rapid (reading in 15 min) and painless. They allow for testing several molecules simultaneously in one session. Positive controls are added either to histamine or codeine sulfate, and a negative control (saline solution), allowing for:

- elimination of false positives (dermographism)
- elimination of false negatives (in subjects under treatment with corticosteroids or antihistamines)

The skin test is considered positive when the diameter of the wheal is equal to 50% of the positive control or is equal to 3 mm\(^{27}\).

**Intradermal test allergy reactions**

Intradermal tests (IDT) are easy to perform and no specific material is needed. This is a prolonged test (every reaction must be read 15-20 minutes after the injection, before increasing the concentration of the allergen) and is painful for the patient. The test is performed on the forearm, arm or back. An IDT is positive when the diameter of the wheal is 9-10 mm.

The sensitivity of the skin tests is excellent for the muscle relaxants (97%) and its specificity is almost absolute. This is conditioned by having performed through IDT the concentrations without exceeding 10 of the commercial solution (there is risk of nonspecific release of histamine for higher concentrations). Its sensitivity is more uncertain for barbiturates, benzodiacepines and morphinics. Concordance of the IDT with muscle relaxants is excellent, close to 97%, and its reproducibility is about 88 percent\(^{2}\).

In practical terms the allergological profile must include at least two types of tests to be reliable. A positive profile should prompt to eliminate the drug. The allergologist must deliver a complete clinical history to the patient and to the anesthesiologist. A negative profile after an anesthetic accident should be renewed 3 months later. If it is negative again, one should consider a non-specific release of histamine. However, this diagnosis is never accurate and does not protect against future accidents.

**Preanesthetic medication**

The objective of preanesthetic medications is to prevent the consequences of the release of histamine due to the blockage of its receptors. The preanesthetic medication cannot prevent a true anaphylaxis reaction, the antihistamine drugs are the basis for such prevention. The drugs that inhibit the synthesis of histamine or the degranulation have not yet proven its efficacy.

Hydroxiceine is among the Anti-H1 antihistamines that should be preferred. This drug has actual antihistamine properties along with sedative and ansiolic effects. It is pre-
scribed orally 1-2 hours before beginning the surgery as well as the night before (1.5 mg/kg).

Use of Anti-H2 antihistamines is more controversial. Its use is recommended in the European literature, although its actual benefit has not been established. Its efficacy has not been formally proven and these drugs have potential secondary deleterious effects.

Regarding the drugs that inhibit the activation of the complement (epsilon aminocaproic acid and tranexamic acid) these are indicated in cases of allergy to iodinated contrast media. These drugs have two absolute contraindications: thrombosis and pregnancy. It is worth taking into account that despite administration of these drugs, lethal anaphylactic shocks have been described as a consequence of exposure to iodinated contrast media.

ANESTHESIA PROTOCOL

Choice of the anesthetic technique

Whenever possible, locoregional anesthesia should be the method of choice. Allergic reactions to local anesthetics is rare and this method avoids intubation that can provoke bronchospasm in asthmatic patients allergic to muscle relaxants.

Choice of drugs

The halogenated drugs are preferred because these are capable of preventing bronchospasm. The choice of intravenous anesthetics must take into account the molecules that release less histamine (Table II). The drugs should be diluted and slowly injected; high concentrations can provoke non-specific release of histamine.

CONCLUSIONS

Allergic accidents due to anesthetics are not fully preventable despite the advancement in understanding their mechanisms and in progress toward diagnosing allergic responses. Cardiovascular effects secondary to the release of histamine can be effectively managed through appropriate intravascular volume replacement and/or catecholamines, although, the response of every patient will be different.

The new neuromuscular-blocking drugs (rocuronium and cisatracurium) can release less histamine; although, these drugs produce a direct vasodilator response and lead to false-positive results in the intradermoreactions, which in turn will cause erroneous interpretations. The mechanisms involved in the non-immunological release of histamine entail the degranulation of mastocytes via cellular activation and phospholipase stimulation, but not the degranulation of basophiles.

The interview conducted with the patient during the pre-anesthetic consultation is the central element in being able to detect potential problems. In case of an accident or perioperative incident, performing an allergological profile to search for the etiology is required.

There are several questions that will be answered through ongoing research studies:

1. Should intradermoreactions (prick tests) be carried out during the pre-anesthetic consultation in all subjects with moderate risk?
2. Should we avoid the use of muscle relaxants in patients with a history of allergy?
3. Testing of new preventive methods: The techniques of haptenic inhibitors have been already tested with dextranes; is it recommended to test them against muscle relaxants?

REFERENCES