Acute management of perioperative anaphylaxis

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Dear Editor,

Although rare (with estimated incidence in the range of 1:353 to 1:18600 procedures), perioperative immediate hypersensitivity reactions are the most challenging clinical problems requiring drug allergy investigation. They are also a challenge for the surgical team, including the anesthesiologist who manages these cases directly. A combination of multiple anesthetic drugs, chemicals, surgical procedures, hidden exposures, and several differential diagnoses contribute to the challenge, making management of perioperative anaphylaxis complex. Collaboration between anesthesiologists, surgeons, and allergists is essential.[1] The European Academy of Allergy and Clinical Immunology (EAACI) position paper on this subject was important to guide correct investigation and management of these important events.[2]

Proper management of anaphylaxis during anesthesia requires prompt recognition and treatment, quantification of peak serum tryptase, and determination of the responsible agent. Signs and symptoms should be evaluated as well:

– Cardiovascular collapse or cardiac arrest, hypotension with or without tachycardia. Bradycardia may occur if the patient is highly hypovolemic or treated with beta-blockers.
– Bronchospasm is usually present in patients with underlying airway disease, such as asthma or COPD.
– Cutaneous presentation: urticaria, angioedema, and disseminated rash are frequent signs of anaphylaxis, but their absence does not exclude it.
– Gastrointestinal signs and symptoms may be present during regional anesthesia but are not common with general anesthesia, since fasting is required.

Differential diagnoses related to anesthetic and surgical procedures include systemic mastocytosis, mast cell activation syndromes and hereditary alpha-tryptasemia, uncontrolled surgical bleeding, bronchial hyperreactivity, adverse drug reactions, iatrogenic intubation trauma, sepsis, thromboembolic event, cold-induced urticaria/anaphylaxis, and hereditary angioedema (HAE).

Systemic mastocytosis is a rare condition. The rate of immediate reactions related to anesthesia and surgery in patients with mastocytosis is only 0.4%. The physiological stress of surgical procedures and use of anesthetic and multiple analgesic agents, such as neuromuscular blockers and opioids, may be triggers of acute hypersensitivity reactions in this condition. Patients with mastocytosis require careful surgical management, especially when general anesthesia is contemplated. It is important to measure serum tryptase before surgery when mastocytosis is suspected (normal value: <11.4 ng/ mL). Elevated serum tryptase levels have been associated with an increased risk of systemic reactions. Several drugs, including neuromuscular blockers, can potentially activate mast cells through non-IgE MRGPRX2 receptors, thereby inducing mast cell-mediator release and consequently anaphylaxis.[3]

Acute Perioperative Anaphylaxis Management:

– Airway maintenance.
– 100% oxygen administration.
– Intravascular volume expansion.
– Epinephrine administration: preferably intramuscular epinephrine (0.5 mL of a 1 mg/mL solution) at the outer thigh (vastus lateralis muscle). An alternative route is to intravenously administer 1-3 ml of 1:10000 aqueous solution (0.1 mg/mL) over 10 minutes.[4]

Severe reactions may be difficult to treat and epinephrine may be given more than once (sometimes 3 injections), as well as larger doses of catecholamines, volume replacement and close intensive care observation.[5] The American Society of Anesthesiology (ASA) has listed the following risk factors for fatal outcomes related to anaphylaxis: morbid obesity, increased patient age, coronary artery disease, beta-blockers and angiotensin converter antagonists, asthma, and malignancy.[6] It is important to ensure that all possibly implicated factors and allergens are removed, such as chlorhexidine, latex, colloids, and drugs.

Post-anaphylactic reaction management:

– Evaluation of suspension of surgery depending on different factors: patient's physical condition, anaphylactic event severity, surgery status, and the urgency of the procedure. The risk/benefit ratio should always be considered.

– After anaphylaxis is controlled: administration of antihistamines and steroids, checking serum tryptase level, and patient transfer to an Intensive Care Unit.

There is no demonstrated evidence that supports pre-operative systematic screening in general patients. Allergy assessment must be performed in high-risk patients and in patients who have had an anaphylactic event during the perioperative context.[7]

When a cause is found, an adequate alternative should be recommended for drug groups with potential cross-reactivity.[8] In approximately one-third of patients, no culprit could be identified.[9] Suspected drugs should be investigated and when proven to be involved they should be avoided. Antibiotics, especially cefazolin, are among the major causes of IgE-mediated reactions and an elevated baseline serum tryptase level was associated with increased risk of recurrent perioperative allergic reactions.[10]

Despite intramuscular epinephrine being the first-line drug recommended to treat anaphylaxis, its use remains suboptimal. The dose recommended for use by healthcare professionals is 0.01 mg/kg of body weight, to a maximum total dose of 0.5 mg, given by the intramuscular route. Dosing should be repeated every 5-15 min if symptoms are refractory to treatment. Epinephrine administered by the intramuscular route is generally well tolerated. Regarding the intravenous route, arrhythmias can potentially occur because of bolus administration of epinephrine. For this reason, the intravenous route is not recommended for initial treatment of anaphylaxis and, if used, it should be administered to monitored patients by personnel experienced in diluting and administering the correct doses and should preferably be given as an intravenous infusion via an infusion pump. A number of protocols exist for low-dose epinephrine infusions via a peripherally-sited cannula to treat reactions refractory to intramuscular epinephrine. In Australia, New Zealand, and Spain these protocols are being developed as part of these countries' national anaphylaxis guidelines and have an excellent safety and efficacy profile. In case of upper airway obstruction, consider adding nebulized adrenaline.[11-13]

Second-line medications include beta 2-adrenergic agonists, glucocorticoids, and antihistamines. Local guidelines may indicate different drugs according to availability.[14] The use of H1- antihistamines has a limited role in treatment of anaphylaxis, but they can be helpful in relieving cutaneous symptoms. Second generation antihistamines may overcome unwanted side effects such as sedation, which may be counterproductive in anaphylaxis, but first generation H1-antihistamines are currently the only class available for parenteral use (e.g., chlorpheniramine, diphenhydramine, promethazine, clemastine). Rapid intravenous administration of first-line antihistamines such as chlorpheniramine could potentially cause hypotension. Antihistamines are now a third-line treatment in some guidelines, due to concern that their administration can delay more urgent measures such as repeated administration of intramuscular epinephrine. Glucocorticosteroids are commonly used in anaphylaxis, with the goal of preventing protracted symptoms, especially in patients with asthmatic symptoms, and also to prevent biphasic reactions (intravenous hydrocortisone or methylprednisolone). However, there is increasing evidence that glucocorticosteroids may be of no benefit in the acute management of anaphylaxis, and may even be harmful, so their routine use is currently controversial.[15,16] Parenteral administration of glucagon may be used in patients with anaphylaxis with no optimal response to epinephrine, in patients taking beta-blockers, despite very limited evidence. Glucagon may have a role in anaphylactic cases associated with severe inotropic cardiac dysfunction.[17]

Around half of biphasic reactions occur within the first 6-12 h following an anaphylactic reaction. Patients with anaphylaxis need to be observed: this is important especially in severe reactions, and in those requiring multiple doses of epinephrine.[18,19]

A follow-up investigation should be conducted after a perioperative immediate hypersensitivity event to establish a diagnosis and to provide advice for subsequent anesthetics. The main risk factor for perioperative IgE-mediated anaphylaxis is a previous uninvestigated perioperative immediate hypersensitivity reaction.

The concept of cross-reactivity between drugs used in the perioperative setting and foods is often quoted, but is usually not supported by evidence. There is no reason to avoid propofol in egg, soy, or peanut allergy. The allergenic determinants have been characterized for fish, shellfish, and povidone iodine, but remain unknown for iodinated contrast agents. Iodinated contrast agents may be used in seafood allergy. Evidence supporting the risk for protamine allergy in fish allergy and in neutral protamine Hagedorn insulin use is lacking. Cross-reactivity to gelatin-based colloids may occur in α-gal syndrome.

Atopy and allergic asthma and non-allergic conditions, such as NSAID-exacerbated respiratory disease, chronic urticaria, mastocytosis, and hereditary or acquired angioedema are not risk factors for IgE-mediated drug allergy, but there is a perioperative risk associated with the potential for clinical exacerbation of these associated conditions.[20]

Most patients safely undergo subsequent anesthesia after a proper Allergy and Immunology evaluation. Cooperation between anesthesiologists and allergists/immunologists is of extreme importance for a successful approach in the diagnosis, investigation, and management of perioperative anaphylaxis.[21]

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