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REVIEW

Perioperative anaphylactic reactions: Review and procedure protocol in paediatrics

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Abstract Perioperative anaphylactic reactions are immediate, hypersensitive reactions that are potentially life-threatening resulting from a sudden release of mediators from mast cells and basophiles, due to either immune (IgE or non-IgE mediated) or non-immune mechanisms. The most frequent causing agents are neuromuscular blocking agents (NMBAs), latex and antibiotics, with latex being the first cause in paediatrics. With regard to perioperative anaphylactic reactions, the usual early signs and symptoms of an anaphylactic reaction could be overlooked or erroneously interpreted and non-severe anaphylaxis could go undetected, with a risk of more severe reactions in the future. Using the data registered on the anaesthesia sheet, it is essential to establish a chronological relationship between drugs and/or substances administered and the reaction observed. An elevated level of tryptase confirms an anaphylactic reaction, but this does not usually increase in the absence of compromised circulation. An allergy study should be carried out preferably between 4 and 6 weeks after the reaction, using a combination of specific IgE, skin and controlled exposure tests (if indicated). Test sensitivity is good for NMBAs, latex, antibiotics, chlorhexidine, gelatine and povidone, and poor for barbiturates, opiates (these can give false positives since they are histamine releasers) and benzodiazepines. Special preventive measures should be taken, especially in the case of latex. We present the maximum concentrations recommended for skin tests, the recommended dosage to treat anaphylactic reactions in paediatrics and a procedure algorithm for the allergological study of these reactions.

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Review

Introduction

Perioperative anaphylactic reactions are potentially life-threatening, immediate, hypersensitive reactions. The European Academy of Allergy and Clinical Immunology (EAACI) and the World Health Organization propose that these anaphylactic reactions be classified as allergic anaphylaxis (immune) rather than non-allergic (known to date as anaphylactoid or pseudoanaphylactic).[1] All these are a result of the release of pre-formed and newly synthesized mediators from the mast cells and basophiles.

Many of the drugs or substances used in perianaesthesia can provoke adverse reactions related to their pharmacological properties (usually dose-dependent), or unrelated to the same (less dose-dependent), with the latter corresponding to: intolerance, idiosyncratic and anaphylactic reactions (immune or non-immune).

Prevalence

The estimated incidence of perioperative anaphylactic reactions in Spain is one in every 10,263,[2] and in other countries this varies widely between 1/1700 and 1/20,000.[3] In many of these series, immune reactions represent 60% of all hypersensitive reactions observed during the perioperative period, with a mortality rate of between 3 and 9%.

Mechanism

Anaphylaxis is a potentially lethal, acute, multi-systemic syndrome, resulting from the sudden release of mediators into the circulation by mast cells and basophiles.[4] Perianaesthetic anaphylaxis can be produced by the following mechanisms[1]:

- IgE mediated mechanism, which represents approximately 60% of cases.
- Non-IgE mediated, immunologically caused (non-IgE mediated immunological anaphylaxis, formerly known as anaphylactoid reactions), with reactions mediated by IgG or IgM being included in this category, or by antigen-antibody plus complement complexes.
- Non-immunological direct release of histamine and other mediators from mast cells and basophiles.

Allergic anaphylaxis is caused by the interaction of an allergen with IgE. In sensitised individuals, these antibodies are bound to high affinity receptors in mast cells and basophiles and to low affinity receptors in lymphocytes, eosinophiles and platelets. Pre-formed and newly synthesized mediators are released such as: histamine, tryptase, PG2, leukotrienes, thromboxane A2, platelet activating factor, chemokines and cytokines, which explain the clinical findings.[5] Allergic anaphylaxis to some substances such as dextrans can be caused by IgG immunocomplexes with the antigen, which activate the complement's system.

The mechanisms of non-immune reactions are not well established, but they are considered to be a result of the direct stimulation of mast cells and basophiles with mediator release.[5]

On the other hand, several causing agents such as neuromuscular blocking agents (NMBAs) are capable of causing a reaction via more than one mechanism.[6]

Whatever the mechanism, the initial management of the reaction is the same, and the clinical severity similar, even though some differences can be appreciated between the different causing mechanisms[7]:

- Only IgE mediated reactions can be studied with skin tests.
- The severity of IgE mediated reactions can increase with the subsequent administration of the causing agent, whilst the others remain similar.
- The frequency or intensity of non-IgE mediated reactions (*e.g. contrast reactions*), can be reduced with pre-medication.
- Non-IgE mediated reactions do not require previous contact with the substance. This is generally required for IgE mediated reactions, although there are cases where this happens on first contact, which could be due to a cross-reaction with other substances to which the patient is sensitised.

Causing agents

Even though numerous possible causing agents exist, the cause cannot be identified in a significant number of cases. The best data concerning perioperative anaphylaxis come from the series pertaining to a French multi-centre study (started around the mid-1990s and currently on-going).[3,8]

NMBAs are the most common agents, being the most frequently involved substances, ranging between 50 and 70%, followed by latex (12–16.7%), and in recent reports, by antibiotics (15%).[3]

Neuromuscular blocking agents

These can cause anaphylaxis either by IgE-mediated mechanisms or by non-immunological direct activation of the mast cells, with the IgE mediated reactions being the most severe.

Groups of tertiary and quaternary ammonium are the principal components of these drugs' allergenic sites.[3] Crossed-sensitivity is frequent (between 60 and 70% of cases) and this is believed to be due to the shared quaternary ammonium group.[9]

Cross-reactivity to all is unusual, with this being more frequent between those of the same group, although this can also occur between different groups of NMBAs and can also happen more frequently between NMBAs, *aminosteroids* (*pancuronium, vecuronium, rocuronium*), than with *benzylisoquinoline (D-tubocurarine, atracurium* and *mivacurium*).[3]

Suxamethonium (depolarising blocker, succinylcholine), is the most implicated in anaphylactic reactions, followed by *atracurium* and *rocuronium*.[10] Between 20 and 50% of reactions to relaxants are of non-immune origin, with these generally being less severe than IgE-mediated ones, except in a sub-group of hyper-responders to released histamine and they occur, above all, with *benzylisoquinoline* derivatives (*tubocurarine, atracurium and mivacurium)*.[11]