

Allergic Reactions in the Perioperative Period in Children

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Abstract

Background: There have been reported some reviews and position papers of international societies concerning to perioperative hypersensitivity reactions in adult patients, However the information in the pediatric patient is very limited.

Objectives: Updated review on the identification, diagnosis and management of perioperative hypersensitivity reactions in pediatrics.

Methods: Search of the literature from 1980 through Medline database.

Results: The correct treatment of perioperative hypersensitivity reactions are based on the suspected diagnosis, signs and symptoms, and time of occurrence. Latex, neuromuscular blocking agents (NMBA) and antibiotics are most often associated with immediate hypersensitivity reactions in anesthetic / surgical events. The Ring-Messmer classification can help to categorize perioperative hypersensitivity reactions and provide proper treatment. The adrenaline is the first-line drug in the management of hypersensitivity reactions grade II or higher by Ring-Messmer classification/ or when the patient meets clinical anaphylaxis scenarios; adrenaline administration and aggressive fluid therapy as first-line treatment is responsibility of surgeons and anesthesiologists. Late assessment corresponds to the allergist / clinical immunologist to discern the hypersensitivity mechanism, confirm a diagnosis, and provide prevention setting applicable to each patient.

Conclusion: Pediatric perioperative hypersensitivity reactions are rare but with serious consequences. Unlike the adult patient, the latex is the most common agent, therefore, reduction in use becomes a preventive measure.

Keywords: Hypersensitivity; Allergy; Pediatric anesthesia; Skin tests; Adrenaline

references were obtained, and additional bibliography, cited by the authors of the preselected articles, was also revised.

Introduction

Perioperative allergic reactions constitute a real surgical emergency and is one of the few clinical situations in which death can be attributed directly to the drugs or agents used in anesthesia or surgery [1]; its treatment depends on the anesthesiologists, pediatricians, surgeons and other health workers involved in surgery. A large number of surgeries are performed daily, and the inherent risk involved in these surgical procedures to develop hypersensitivity reactions is indisputable, many papers have been published by international societies and colleges, most of them are focused on adult patients [2-6], however, information on pediatric patients is scarce [7]. This article had the purpose of review current information on perioperative allergic reactions in pediatric patients.

Methodology

A bibliographic search was carried out using the Medline database, using the key words: allergy, anesthesia, hypersensitivity, immediate hypersensitivity, pharmaceuticals, drugs, primary prevention and pediatric anesthesia, searching for original papers, contained in indexed journals from the last 30 years in English and Spanish. 46

Definitions

The North American and European multidisciplinary working group has defined several terms for actual use, that allow a better classification of the adverse reactions:

Hypersensitivity encompasses a general concept that includes all objective and reproducible responses initiated by exposure to an agent, that does not cause a reaction in subjects who are healthy in all other aspects; this concept does not infer the physiopathological mechanism, but classifies responses in allergic and non-allergic hypersensitivity [8].

Allergic hypersensitivity reactions include those onsets by immunological mechanisms, and can be classified, by those that are immediate, mediated by antibodies (most frequently by IgE) produced in a period no longer than an hour after being exposed to the causal agent, and those that are delayed produced by cellular mechanisms.

Anaphylaxis is considered to be the most severe clinical manifestation of the immediate hypersensitivity reactions, which can quickly endanger the patient's life.

Risk factors

During daily practice, the pediatric patient with a history of other allergic diseases should not be characterized a priori as high risk; the health professional should, facing the medical history, investigate the type of conditions, clinical characteristics of the allergic disease and its triggers in order to identify if there is a probable or identified allergens that contraindicate the procedure. The precedent of food allergy does not per se imply a change in the anesthesia technique, unless the change is determined after the perioperative evaluation.

Epidemiology

After the literary search, all that could be identified was one prospective and multi-centric epidemiological study on the immediate hypersensitivity reactions during anesthesia or perioperative events in children [9], and a retrospective study on 68 cases of immediate hypersensitivity reactions in pediatric patients, over a 12 year period. The remaining publications are reports from international societies concerning adult patients [10-12].

The frequency of perioperative anaphylaxis in Mexico isn't known with precision. In Europe, the reported incidence ranges between 1/10,263 patients in Spain and 1/1700 to 1/20000 in other countries. In France, perioperative anaphylaxis is estimated at less than 5% of patients between 0-10 years of age, and less than 10% between those between 10 and 19 years of age [10,13,14]. Immune-mediated reactions represent 60% of all perioperative hypersensitivity reactions, with a mortality rate between 3-9%, [15,16].

Only 12 publications have been made since 1982 concerning cases of anaphylactic reactions during anesthesia in surgery caused by antibiotics, antiseptics, neuromuscular blockers or analgesics [17-27]. However, there are more than 100 reports of perioperative anaphylactic reactions attributable to latex [28-43].

Involved allergens

In adult patients, neuromuscular blockers are the most frequently involved drugs (62%), followed by latex (27%), plasma derivatives (14%), hypnotics (12%) and opiates (9%)[11]; among other cases, hypersensitivity has been reported with: muscle relaxants (succinylcholine, benzylisoquinoline), as well as other drugs (ketamine, cefuroxime, lidocaine, chlorhexidine). Data concerning the frequency of these agents on children were not found, however, we know that latex is the first cause of perioperative anaphylactic reactions, with an incidence of 1/10,159 anesthetic events [44].

Special Considerations Concerning Involved Agents

Neuromuscular blocking agents (NMBAs)

Its reactions can be mediated by IgE or by non-immunologic activation directly to the mast cells. Between 20-50% of reactions to muscular relaxants have non-immunologic origins, these reactions are less severe; the drugs most commonly associated to these reactions are benzylisoquinolines [45].

Concerning reactions mediated by IgE, the tertiary and quaternary ammonium groups are identified as the key allergenic determinants [16]. The cross-reactivity for all agents is rare, and more frequent between NMBAs from the same group, commonly among aminosteroids (pancuronium, vecuronium, rocuronium) and

benzylisoquinolines (D-tubocurarine, atracurium and mivacurium) [46].

Cases of anaphylaxis or IgE mediated reactions have been reported from the first exposure to the drug, inferring sensitization due to cross-reactivity with other substances containing similar tertiary or quaternary ammonium structures [16], such as pholcodine present in several antitussives or dental hygiene products, however, evidence concerning *in vivo* and *in vitro* situations is controversial [47].

Antibiotics

Antibiotics are frequently administered preoperatively. Beta-lactams cause around 70% of the hypersensitivity reactions attributable to antibiotics in perioperative events [48]. Vancomycin has also been associated to perioperative reactions in some cases, although most are non-immunologic (red man syndrome) [49]. Quinolones are the third cause of reactions to antibiotics, nevertheless, its use in pediatrics is limited [50]. Bacitracin and rifampicin have also been reported as causal agents, especially facing topical treatments for wounds, which may potentially cause immediate hypersensitivity reactions [16].

Hypnotics (inductors)

Responsible for 2% of all perioperative reactions. Due to the origin of these drugs, they can be classified into two groups: barbiturates and non- barbiturates.

1. **Barbiturates:** Represented by thiopental, it is currently responsible for less than 1% of perioperative hypersensitivity cases [51], its occurrence is uncommon, estimated at 1/30 000 anesthetic events; and is primarily responsible for reactions during induction, most of which are IgE mediated.

2. **Non-barbiturates:** Including benzodiazepines (midazolam), propofol, etomidate, ketamine and inhaled anesthetics. Although it is a larger group, hypersensitivity reactions to these drugs are rare; many reactions are believed to be related to their histamine releasing capacity through direct effector cell stimulation. Concerning propofol, specifically, it is responsible for less than 2% of hypnotic reactions. Up till now, no reactions to inhaled hypnotics have been reported [48].

Opiates

The immunological reactions to morphine, codeine, meperidine, fentanyl and derivatives are rare. Derived from the intrinsic properties of these drugs to release histamine by mast cells (especially morphine), the distinction between anaphylaxis and mediator release by non-immunologic mechanisms is not always simple [8,52].

Opiates typically cause skin symptoms; the drug joins the opiate receptors in the mast cell, in this way releasing histamine and other mediators, thus generating erythema, hives and angioedema [53].

Local anesthetics

This group of drugs are derivatives of the amino group and benzoic acid esters. Hypersensitivity reactions are infrequent and less of 1% of these seem to have an immunologic mechanism [54]. The most common causes are inadvertent intravascular injections or systemic absorption of epinephrine when this agent is combined with local anesthetics. The reactions can be similarly attributed to commercial preservatives (methylparabens, parabens, o metabisulphite) [48,55].

The para-amino group (procaine, tetracaine, etc.), has a greater capacity for causing reactions through immunologic mechanisms than the amide group (lidocaine, bupivacaine, mepivacaine); nonetheless, its frequency is estimated at less than 0.6% [48].

Other agents

This diverse group is responsible for less of 5% of perioperative anaphylactic reactions. Chlorhexidine, for example, can manifest hypersensitivity reactions after insertion of the central catheter impregnated with the agent, or when the agent is in contact with the mucous membrane, such as positioning urethral catheters or even topical application [56,57]. Rare cases of anaphylaxis due to topical agents have also been described, such as Iodopovidone [58].

Other involved agents include: radiographic contrast agents, blood product transfusions, especially in cases of severe IgA deficiency, sulphites, Non-steroidal anti-inflammatory drugs, bacitracin found in some irrigation solutions, ethylene oxide when used as sterilizer, streptokinase and urokinase, insulin, heparin, hyaluronidase and neostigmine [59].

Latex

Latex fluctuates in two series between the two main causes of perioperative anaphylaxis in children; especially in patients who faces multiple surgical events, particularly in the risk group where it clearly becomes the agent most related to perioperative anaphylaxis [44,48].

Multiple risk factors in children have been associated to latex allergies, as atopy (genetic susceptibility for specific IgE synthesis facing low allergen concentrations) [60,61], age at the moment of exposure, the number of procedures and the type of pathology.

It has been observed that the risk of latex allergies is higher when 8 or more surgeries have been practiced in the first year of life of the patient [62], reaching even higher levels of risk when concerning patients with esophageal atresia or spina bifida, where two surgeries have been seen to be enough to cause sensitization towards this agent, one event for esophageal atresia and a minimum of four surgeries in those presenting a urological malformation [44].

Patients at Risk of Perioperative Anaphylaxis

Despite the age of the patient, the risk does not differ from what can be observed in adults, three groups of patients with risk of perioperative anaphylaxis have been defined. These groups correspond to:

- Patient presenting signs or symptoms suggesting a hypersensitivity reaction in the immediate perioperative period and who has not benefitted from a diagnostic test.
- Patient presenting clinical symptoms suggesting an immediate allergy when is exposed to latex (whichever be the circumstances of exposure) or by ingesting fruit or vegetables with cross-reactivity to latex (avocado, kiwi, banana, chestnut, papaya, pineapple) through latex-fruit syndrome [61].
- Patient presenting multiple surgical events.

The evaluation between these different groups of risk patients by allergist or clinical immunologist is recommended [63-66].

Diagnosis of Immediate Perioperative Hypersensitivity Reactions

The description of the signs and symptoms and the onset reaction time concerning the introduction of the allergen is the first key element in the diagnosis algorithm.

Anaphylaxis can be observed at any time during anesthesia. When the allergen is a medication of intravascular administration, the clinical expressions are produced in the first minute(s) following the administration [67,68]; nevertheless, when the allergen is latex, the clinical expressions may be produced belatedly, with the appearance of symptoms in the induction of anesthesia with a median interval between 30 minutes; less frequently, the reaction to latex may appear before the induction of anesthesia [67], this early start is probably related to the level of sensitization to latex and its exposure before surgery [68].

Ring and Messmer postulated a classification to stratify the clinical response in to four degrees of severity to describe the intraoperative immediate hypersensitivity reactions [69,70] (Table 1), which although were described for colloid agents and do not differentiate the implied physiopathologic mechanism, have been adopted in several countries [71].

Degrees	Clinical signs
I	Mucocutaneous signs: erythema, hives, with or without angioedema
II	Moderate affectation to multiple organs: cutaneous signs ± mucus membrane ± low blood pressure ± tachycardia ± coughing ± dyspnea ± digestive symptoms
III	Mono or multi visceral affectation: circulatory collapse ± tachycardia or bradycardia ± Cardiac arrhythmias ± bronchospasms ± mucocutaneous signs ± digestive symptoms
IV	Cardiac arrest

Table 1: Ring and Messmer classification where immediate hypersensitivity reactions are stratified according to their clinical severity [70].

In a study by the French Society of Pediatric Anesthetists, the clinical signs most frequently reported were: low blood pressure (with a decline of over 30% for blood pressure values regarding the 95th age percentile) associated to tachycardia (81%), bradycardia (14%), bronchospasms (62%) and skin symptoms (67%) [69].

Among the published clinical cases, the clinical signs were more frequent during the induction of anesthesia, immediately or a few minutes after administering the responsible drug intravenously or after the topical application of the drug (Chlorhexidine) (Table 2). The cardiovascular signs (bradycardia, low blood pressure, hemodynamic shock) were present in grade III reactions [17-26,72,73]. In children, the most frequent symptoms were respiratory (coughing, wheezing, bronchospasms, respiratory insufficiency), contrary to the data reported in adults, where the frequency was equivalent to only 40% in perioperative anaphylactic reactions [48]. The observable difference in respiratory symptoms is due, to patient atopy (where coexistent allergic asthma could be associated), which was observable in some cases and could undervalue the risks of the patient [20,21]. Likewise, emphasizing latex as a volatile allergen could favor respiratory signs, such as bronchospasms. Skin lesions (localized or generalized

erythema, hives with or without angioedema) were expressed alongside signs in other systems [17-19,21,23,24,72,73].

Reference	Presumptive allergen	Laboratory studies	Skin test	Comments
Levy et al.	Meperidine	Serum IgE vs. meperidine	Unrealized	Diagnosis only confirmed by serum antibodies and clinical circumstances, the technique is not validated for this drug.
Pollock et al.	Atracurium	Total IgE: <5 U/ml.	Unrealized	Diagnosis is not confirmed, established as probable clinical circumstances.
Baird et al.	Mivacurium	Tryptase: 0.9 U/l (N<0.5).	IDT mivacurium: +, IDT succinylcholine, d-tubocurarine, atracurium, vecuronium, pancuronium, propofol, thiopental and fentanyl -.	Anaphylaxis to mivacurium confirmed no cross-reactivity with other agents.
Ryckwaert et al.	Aprotinin	Tryptase: 18 mcg/l (N<12.5) Histamine: 2 mcg/l (N<0.2) Serum IgE vs. Aprotinin Serum IgE vs. thiopental, atracurium, fentanyl, latex.	ST aprotinin +, ST thiopental, opiates, NMBA & latex -.	Anaphylaxis to aprotinin confirmed.
Briassoulis et al.	Cis-atracurium	Tryptase: 13.6 mcg/l (N<12) Histamine: 11.6 nmol/l (N<9) Serum IgE vs. thiopental & cis-atracurium y QA.	Unrealized	Anaphylaxis likely to cisatracurium not confirmed by skin tests. The concentrations of histamine and tryptase are discretely increased due to making products occurred in a very short period of onset of symptoms.
Legros et al.	Atracurium	Tryptase 19 mcg/l (N<2) Histamine: 89 nmol/l (N<11).	ST cis-atracurium +, IDT to NMBA +.	Anaphylaxis to atracurium confirmed and polysensitization other NMBA.
Prosser et al.	Cefuroxime	Tryptase 200 mcg/l (N<16) Serum IgE vs. penicillin's Serum IgE vs. latex.	ST Cefuroxime +, ST drugs and anesthetics -.	Anaphylaxis to cefuroxime No cross-reactivity study reports to other b-lactams.
Chiu et al.	lidocaine	None	Unrealized	Anaphylaxis to lidocaine unlikely because of the timing and onset of symptoms. No confirmation by ST.
Boynes et al	Midazolam Ketamine	None	Positive reaction to ketamine No details of the test specified midazolam	Anaphylaxis to ketamine unconfirmed Midazolam participation doubtful.
Ferrarini et al.	Chlorhexidine	None	Unrealized	Anaphylaxis to chlorhexidine not confirmed by ST probable diagnosis because clinical history.
Momeni et al.	Aprotinin	None	Unrealized	Anaphylaxis to aprotinin not confirmed by PC, probable diagnosis by clinical history.

IDT (intradermal test), ST (skin test), + (positive), - (negative), N (normal), NMBA (Neuromuscular blocking agents), QA (quaternary ammonium).

Table 2: Summary of diagnostic evaluations in different clinical cases

The reactions attributable to latex were published among the most severe, grade III or IV, including cardiovascular events (low blood pressure, hemodynamic shock associated with tachycardia and bradycardia, and even cardiac arrest). These cardiovascular signs were mostly associated to respiratory symptoms (wheezing, bronchospasms) and sometimes to mucocutaneous signs [12,28,29,31-37,39-41,74,75].

Despite the clinical expressions, immediate drug induced hypersensitivity diagnosis only reached presumptive diagnosis, reaching an accurate diagnosis in half the cases. (Table 2) [17,18,20,23,24]. Also, when the reactions were related to latex, most

reports were carried out using an adequate allergological evaluation [12,28,29,32-34,36,37,39-41,74].

In adults, three predictive factors were identified concerning the severity of an immediate hypersensitivity reaction [68]. These markers can be associated or isolated:

- The early onset of the reaction: the clinical manifestation of a more severe reaction is generally observed seconds to minutes after the early introduction of the allergen.

- The absence of mucocutaneous symptoms (such as erythema or hives), sometimes it may be due to peripheral hypoperfusion; these signs after the normalization of perfusion.

- Presence of bradycardia in quick succession after initial tachycardia. This expression of paradoxical bradycardia in hypovolemic shock, or the Bezold-Jarisch reflex, is one of the last compensatory mechanisms for maintaining ventricular filling in a hypovolemic patient.

These markers could be applied to pediatric patients. Among the reported cases on anaphylaxis, the time is the key, administration should be investigated, whether intravenous or topical, the time of onset of symptoms (with an average of 3 minutes from administration to the appearance of clinical signs) [17-20,22, 23,26,73]. A lack of mucocutaneous signs in five severe reactions was observed [12,14,16,20,36]. In the French Society's study, bradycardia in 14% of the cases was also reported, but it wasn't specified whether it was related to circulatory collapse and/or secondary hypoxia [69].

	Drugs	Concentration (mg/ml)	Dilution for Prick	Cmax (mg/ml)	Intradermal dilution	Cmax (mcg/ml)
NMBA	Atracurium	10	1/10	1	1/1000	10
	Cisatracurium	2	Undiluted	2	1/100	20
	Mivacurium	2	1/10	0.2	1/2000	10
	Pancuronium	2	Undiluted	2	1/50	40
	Rocuronium	10	Undiluted	10	1/200	50
	Suxamethonium	50	1/5	10	1/100	40
	Vecuronium	4	Undiluted	4	1/10	400
Hypnotics	Etomidate	2	Undiluted	2	1/10	200
	Diazepam	5	Undiluted	5	1/50	100
	Midazolam	5	Undiluted	5	1/10	500
	Propofol	10	Undiluted	10	1/10	1000
	Thiopental	25	Undiluted	25	1/10	2500
	Ketamine	100	1/10	10	1/100	1000
Opioids	Alfentanil	0.5	Undiluted	0.5	1/10	50
	Fentanyl	0.05	Undiluted	0.05	1/10	5
	Remifentanil	0.05	Undiluted	0.05	1/10	5
	Morphine	10	1/10	1	1/1000	10
Others	Heparin		Undiluted		1/10	

	Concentration	Dilution	1/100	1/10	
Gelatin		Undiluted	1/100	1/10	
Chlorhexidine	50	1/10	5		20
Yodopovidone	25	Undiluted	25	-	-
Methylene blue	10	Undiluted	10	1/100	100
Iodinated contrast media	Undiluted		1/10		
Metamizole	400	Undiluted	400	1/4000	100
Vancomycin	50	1/1000	0.05	5 x 10 ⁵	0.1
Amoxicillin/Ampicillin		20		20 x 10 ³	
Benzyloxy penicillins		1/1000 UI		10 000 U	
Local anesthetics	Undiluted		1/10		

Modified of ENDA/EACI Drug Allergy Interest Group position paper, 2013. [83]

Table 3: Nonirritating concentrations recommended for skin tests.

Performing the Diagnosis

The initial diagnosis on immediate perioperative hypersensitivity should be based on the recognition of clinical signs and where relevant, confirmed through an allergological assessment, which implies carrying out sensitization or serum skin tests.

Laboratory tests

Clinical/lab tests are the second element from the diagnosis algorithm concerning immediate hypersensitivity reactions. Once the clinical situation of the patient has been stabilized, the extraction of blood products can be carried out so as to confirm the events. Whether through cell activation tests (mast cells, basophils), or the determination of serum concentrations of histamine or tryptase (according to their availability and time).

Histamine is a preformed inflammatory mediator contained by mast cell and basophil intracytoplasmic granules. A peak in the hypersensitivity reaction during the first minutes indicates the activation of these cells; this marker is not specific, its increase is observed during allergic reactions and certain non-allergic reactions. The average plasmatic lifespan of histamine is short (15-20 minutes). It is why the blood sample should be taken within the first 30 minutes of the reaction [4,5,7]; in the case of grade III or IV reactions, there are trials that have shown that the concentration of histamine in plasma can increase two hours after the reaction, due to probable enzyme metabolism saturation and allowing the detection during this period of time [48]. Conversely, the normalcy of the histamine concentration doesn't exclude a non-immunologic allergic mechanism [76].

Tryptase is a preformed serine protease enzyme contained mainly in the mast cell granules [55]. The tryptase serum concentration reaches its highest peak between 15-90 minutes and has an average lifespan of 120 minutes [77]. It can be measured between 15-180 after an

immediate hypersensitivity reaction [1,3]. An increase in the tryptase concentration further supports the mast cell activation, but its absence does not exclude the anaphylaxis diagnosis [78]. The value of normal tryptase is variable depending on the laboratory.

Skin tests

These tests make up the third element of the immediate perioperative hypersensitivity diagnosis algorithm. Skin tests, due to their immediate replication and consistency with IgE dependent mechanisms, are the gold standard of diagnosis. The purpose of conducting these tests is to identify the reaction's physiopathological mechanism, and obviously the responsible allergen [8,79].

How to carry out skin tests on a pediatric patient

In children, skin tests (ST) are performed with the same technique of the skin prick test through a drop of each drug used in the anesthesia, just as it is done with adults. The drugs may be diluted or not in 1/10 proportions, as in the case of histamine releasing drugs (mivacurium, atracurium, morphine, vancomycin, etc.). The ST results are always based on the controls: negative control (glycerinated solution) and positive control (histamine 10 mg/ml). The ST can be done on the forearm or on the back, depending on the visible area. The space must be large enough to avoid misreading the test, especially in children because their skin is particularly reactive. The ST should be considered positive if after 15 minutes a hive of at least 3 mm/diameter larger than that caused by the negative control appears [4,79].

If the ST is negative, an intradermal test (IT) should be performed. The IT corresponds to the administration of the drug in the dermis, with a volume of 0.02 - 0.03 ml. The IT will be considered positive if 15 minutes after, the papule diameter is at least equal to or greater than twice the papule was formed during injection [4,79]. The concentration of the drugs used on children is the same as that used on adults (Table 3).

When to carry out skin tests

The ST should be performed 4-6 weeks after the clinical reaction by a physician specialized in allergy and clinical immunology. The period is often necessary due the energy observed in patients after an immediate immunologic reaction. In case of emergency or urgent diagnosis is required, tests may be performed before the period previously mentioned, with safety that the reactivity of the skin is manifested by the positive and negative controls before carrying out the test, although the risk of false negatives should be taken into account.

How to Test

Latex

Latex is tested by ST, using commercial extracts. In atopic patients, it has been recommended to do the test on the distal region of the forearm so as to minimize the risk of lymphatic dissemination. The positivity of latex via ST takes its diagnostic value from the context of the examination and medical history concerning perioperative reactions, the sensitivity and specificity of the latex ST is close to 100% [79].

Neuromuscular blockers

Sensitivity is reported at above 95% and they show remarkable specificity concerning tests in general (ST, IT), especially in a patient presenting an immediate reaction from neuromuscular blockers. The maximum concentrations, irritative doses and dilutions depend on each medication (Table 3). High skin reactivity is observed, especially in blockers from the same group, some series register between 60-80% of the cases [68]; therefore, testing should always be interpreted by a specialist in allergy and clinical immunology. Preferably the anesthetist should communicate which drugs should be tested, because if one of the neuromuscular blockers has a negative result from the ST, it shall be used as a therapeutic option in later procedures if should it be needed [46].

Antibiotics

Antibiotics β -lactam: If the ST is positive, an IT is not needed. Generally, the cross-reactivity with other beta-lactams is searched for using ST. If the ST is negative and if the age of the child or the patient's clinical context merits it, a cross-reactivity search can be carried out with other beta-lactams via an IT. The diagnostic value of STs towards beta-lactam antibiotics is high in children presenting immediate hypersensitivity reactions [80].

Vancomycin: The immediate reactions to this antibiotic are generally due to high speed in the administration flow, this clinical entity is also known as red man syndrome [81]. A negative ST and IT allows for the conclusion that the hypersensitivity reaction it not a result of a non-immunologic mechanism, that is a nonspecific release of histamine.

Other available lab tests

Other biological tools have been proposed in clinical practice, but are not available everywhere. Specific IgE serum determination exists concerning certain anesthetic medications (thiopental, propofol), certain antibiotics (amoxicillin, cefaclor, penicillin's G and V) and latex. However, the sensitivity of these serum tests is less than the skin tests. In fact, the positivity of specific IgE serum contributes to the explanation of the reaction mechanism, but does not prove that the drug or suspected agent is responsible for the clinical reaction [4,7,79]. These biological tests should preferably be requested by allergists/clinical immunologists and anesthetists, and should be interpreted by them as well.

Lastly, other diagnostic tests have been suggested, but they shall not be developed in detail in this present review article.

Treatment

During anesthesia, the patient must be monitored and have constant intravenous access. When faced with an immediate hypersensitivity reaction, all contact with the responsible antigen(s) should be interrupted, as well as any medications being administered at the time, unless this is not deemed possible. The airway shall be maintained with oxygen at 100% and the recommended anaphylaxis treatment, whether or not administering intravenous or intramuscular adrenaline in the external quadriceps at 0.01mg/kg/doses every 5-15 minutes, and reevaluate and categorize the patient continuously to carry out advanced pediatric reanimation protocols in case the patient deems it necessary. Other second line medications can be observed in Table 4 [1,16,82].

Identify the immediate reaction / hypersensitivity anaphylaxis: check clinical signs and differential diagnosis.	
General considerations Discontinuation of the drug / substance suspected Assess the airway, breathing, circulation and classifying life-threatening Inform the surgical / anesthetic equipment and activate emergency protocol Provide O ₂ 100% Trendelenburg position	
If classified as clinical stage of anaphylaxis start first-line treatment, if don't, start second-line drugs.	
First-line treatment	
Administer epinephrine	Reaction grade II or higher: I.M. 0.01 mg / kg in concentration 1: 1000 in vastus lateralis of quadriceps. Children maximum 0.3 mg, Repeat every 5-15 minutes if necessary, if several doses of second line (>3 doses) are required to consider start infusion of epinephrine and / or glucagon 1-2 mg every 5 minutes until response (patients b-blocker therapy / ACEI, etc.) as appropriate. If cardiorespiratory arrest act as guides BLS / PALS according to the clinical setting.
Fluid therapy	Manage physiological solution 0.9% / Ringer-lactate 20 ml/kg in the first 5-10 minutes. Repeat up to 40 ml/kg in the first hour if necessary.
Second line treatment	
Glucocorticoids	Hydrocortisone 25-100 Methylprednisolone 1 mg/kg (Maximum 50 mg)
Antihistamines	Chlorpheniramine 2.5-5mg Diphenhydramine 1 mg/kg (maximum 50 mg) Ranitidine 1 mg/kg (maximum 50 mg)
β ₂ - agonists	Inhaled albuterol or if it is persistent bronchospasm with continuous infusion 5-15 mcg/m
Vasopressors persistent hypotension	Norepinephrine 0.05 to 0.1 mcg/kg/min I.V. Vasopressin response 2-10 U until I.V. Epinephrine 0.1-1 mcg/kg/min I.V.
I.M. (Intramuscular), I.V. (intravenous) ACEI (Inhibitors, angiotensin converting enzyme), BLS (Basic life support), PALS (Pediatric Advanced Life Support), [7].	

Table 4: Algorithm and treatment before Perioperative immediate hypersensitivity reaction in pediatric patients

Action protocol

Previous to surgery, the pediatricians and/or anesthesiologists should identify those children at risk before the surgical/anesthetic event. To prevent any reaction, the following is recommended:

1. Latex free environments concerning surgery on children with spina bifida or those being subjected to multiple surgeries, to prevent agent sensitization.
2. Latex allergies should be ruled out considering children allergic to kiwi, banana, avocado and chestnuts (latex fruit syndrome).
3. Concerning children who are allergic to latex, the perioperative medium should be totally latex free.
4. If there are previous perioperative reactions in the patient medical history, it is important to consider which drugs or substances may be used in the following perioperative event, for example:
 - If there is suspicion of an NMBA allergy, to avoid those from the same group, and if previous studies are available, to only use those that projected negative results in the carried out skin tests.
 - To avoid any drug or substance that caused or are suspected to have caused previous hypersensitivity reactions, as well as those that may have cross-reactivity.

5. Propofol can be used on patients allergic to egg, excepting those presenting anaphylactic reactions (due to an unlikely, although possible, reaction to lecithin contained in the medication).

6. Mastocytosis should be discarded in patients who have presented severe or atypical reactions during previous surgeries or who already undergone a negative allergological study. The use of tourniquets should be avoided in patients with known cases of this illness (due to the release of mediators by mast cells exposed to ischemia).

7. Special considerations must be taken concerning asthmatic pediatric patients, who are at higher risk of suffering bronchospasms during anesthesia, which would aggravate the anaphylaxis. It is recommended to avoid the use of salbutamol at least 6 hours before the use of halogenated anesthetics, to avoid the potential risk of arrhythmia or low blood pressure.

Perioperative period (surgery)

Anesthetic record: A precise record must be kept of all medication and administered substances, doses, and time of administration, as well as the time, description, and duration of suspect clinical symptoms and the treatment being carried out. In the case of a suspected anaphylactic reaction, the following is required: intensive monitoring, adequate ventilation and oxygenation, interruption of the drug, substance or solution administration.

Anaphylaxis treatment: The drug to be immediately administered in the case of a type II or more severe reaction should be adrenaline, as previously commented, subsequently, fluid therapy, and the rest of the treatment (see Table 4).

Conclusions

The risk factors, clinical situation of each patient, and the anesthetic record (received substances and medications and the chronological relation of symptoms), allow for better orientation concerning the probable agent. It should also be borne in mind that most reactions present in children are mainly owed to latex, followed by muscle relaxants and antibiotics. It is vital for all those involved in perioperative events to evaluate, classify and take primary, secondary, or tertiary prevention actions in order to reduce present and future risks.

Key Issues

- Hypersensitivity reactions in the perioperative period in pediatric patients are clinical situations associated with high morbidity and mortality.

- The pediatric patient with a history of hypersensitivity reactions in the perioperative period should be evaluated to try to identify the cause of the reaction.

- Latex, antibiotics and neuromuscular blocking agents are more often associated with hypersensitivity reactions with immunological origin in pediatrics patients, although the group of drugs and agents is large.

- The allergological assessment requires the collection of signs and symptoms, timing and progression of these to properly assess the mechanism of hypersensitivity.

- Tests that can be performed to verify the mechanisms of hypersensitivity include skin prick tests, intradermal test, specific IgE in vitro and in some cases basophil activation test.

- The avoidance or changes of certain drugs in subsequent surgical procedures where it is suspected hypersensitivity reactions without adequate allergological assessment not only increases costs, also turn anesthetic / surgical procedures with higher risks.

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