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Review

Management of the child with allergy to non-antibiotic drugs

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Summary. Non-steroidal anti-inflammatory drugs, perioperative drugs, radio contrast media and chemotherapeutics drugs are, after the non-antibiotic drugs, the drugs most commonly responsible for allergic reactions in children. Management is different depending on the drug involved. (www.actabiomedica.it)

Key words: drug allergy, allergy to non-antibiotic drugs, diagnosis

Introduction

According to the World Health Organization, adverse drug reactions (ADRs) are considered as any noxious and unintended response to a medication that occurs at normal doses used for prophylaxis, diagnosis and/or treatment (1). ADRs can be classified as A-type (dose dependent and predictable) and B-type reactions (dose-independent and unpredictable). A-type reactions: toxicity, side effects, interactions with other drugs. B-type reactions: hypersensitivity [a. allergic reactions (immunonological mediated), e.g. IgE mediated or T-cells mediated; b. nonallergic reactions (non immunological mediated), e.g. pseudoallergy, intolerance, idiosyncrasy] (2-3)]. Drug allergies are drug hypersensitivity reactions (DHRs) for which a definite immunological mechanism is demonstrated. When a drug allergic reaction is suspected, DHR is the preferred term. Mechanistically, DHRs can be defined as allergic (Table 1) (4) and non allergic. Allergies to non-antibiotic drugs in child are mainly to non-steroidal anti-inflammatory drugs (NSAIDs), perioperative drugs, radio contrast media, chemotherapeutics drugs (5).

Non-steroidal anti-inflammatory drugs

NSAIDs are commonly used in the pediatric population as antipyretics/analgesics and anti-inflammatory medications. Hypersensitivity (HS) reactions to NSAID in this age group have unique diagnostic and management issues (Table 2, Table 3) (6).

The term selective reactor (SR) (Table 2, Table 3) has been applied for cases in which the clinical manifestation is due to a single drug or single subclass of NSAIDs with good tolerability to other subclasses. In general, this term includes NSAID allergic hypersensitivity reactions.

There are two well-defined phenotypes of selective HS reactions to NSAIDs:

Table 1. Classification of drug allergies

Type of immune response	Physiopathology	Main clinical symptoms	Chronology (after the drug)
IgE mediated	Mast cell, basophil degranulation	Anaphylaxis, angioedema, urticaria, rhinitis, asthma	within 6 hours after the last intake
IgG and complement	IgG and complement-Dependent cytotoxicity	Cytopenia	5-15 days after the start
IgM or IgG and complement or FcR	Deposition of immune complexes	Vaculitis, Serum sickness	7-21 days after the start 7-8 days after the start
Th1 (IFN-γ)	Monocytes inflammation	Dermatitis	within 21 days after the start
Th2 (IL-4 and IL-5)	Eosinophilic inflammation	Maculopapular exanthema DRESS	several days after the start 2-6 weeks after the start
Cytotoxic T cells (perforin, granzyme B, FasL)	Keratinocyte death mediated by CD4 or CD8	SJS/TEN	4–28 days after the start
T cells (IL-8/CXCL8) exanthematous pustulosis	Neutrophil inflammation	Acute generalized	1 to several days

Table 2. Classification of non-steroidal anti-inflammatory hypersensitivity for the child aged (0-10 y) paediatric population

Cross-reactivity	Type	Clinical of reaction	Chronology presentation	Proposed mechanism	Cofactors (influence)
Cross-intolerant reactions (Non-Allergic)	Non-allergic NSAID hypersensitivity (NERD, NECD, NIUAA)	Urticaria, angioedema, dyspnea, rhinitis, conjunctivitis, anaphylaxis	Immediate, usually from minutes to several hours after exposure	COX-1 inhibition	Possible
Non-cross-Intolerant reactions (Allergic)	Selective NSAID-induced urticaria/ angioedema or anaphylaxis (SNIUAA)	Urticaria, angioedema, anaphylaxis	Immediate (<1 h)	IgE-mediated	Unknown
Selective NSAID-induced delayed reactions (SNIDR)	Various symptoms and organs	Delayed onset T- cell-mediated (usually more than 24 h involved after exposure) (e.g., fixed drug eruption, SJN/ TEN, nephritis)		Unknown	

NSAIDs, non-steroidal anti-inflammatory drugs; COX-1, cyclooxygenase 1; SJS, Stevens-Johnson syndrome; TEN, toxic epidermal necrolysis

Table 3. Classification of non-steroidal anti-inflammatory hypersensitivity for the older paediatric population and adolescents (10-19 y)

Cross-reactivity	Type of reaction	Clinical presentation	Chronology	Mechanism	Cofactors
Cross-intolerant reactions, non allergic	NSAIDs-exacerbated respiratory disease	Bronchial obstruction, dyspnea, nasal congestion, (NERD)	minutes-hours after last intake	COX1-inhibition	Asthma, rhinosinusitis rhinorrhea
	NSAIDs-exacerbated cutaneous disease	wheals and/or angioedema (NECD)	minutes-hours after last intake	COX1-inhibition	Chronic urticaria
	NSAIDs-induced urticaria/angioedema/ anaphylaxis (NIUAA)	wheals and/or angioedema and/or anaphylaxis	minutes-hours after last intake	COX1-inhibition (probably)	Unknown
Non-cross Intolerant Reactions, Allergic	Selective NSAID-induced urticaria/ angioedema or anaphylaxis (SNIUAA)	wheals and/or angioedema and/or anaphylaxis	minutes after last intake	IgE mediated	Unknown
	Selective NSAID-induced delayed reactions (SNIDR)	cutaneous and mucous reactions, complex reactions (e.g. SJS/TEN), organ-specific disorders	delayed onset (usually more than 24 hours after last intake)	T-cell mediated	Unknown

a. Selective NSAID-induced urticaria, angioedema, and/or anaphylaxis (SNIUAA): these are immediate reactions, probably mediated by a specific IgE antibody;

b. Selective NSAID-induced delayed type HS reactions (SNIDR): these are reactions occurring within 24-48 hours after drug intake although the interval can be shorter. They are probably mediated by a specific T-cell response.

The term cross-reactor or according to the current classification, cross-intolerance (CI) reactions (Table 2, Table 3), is used in cases where the clinical manifestations are triggered by more than one subclass of NSAIDs, in which pharmacological mechanisms are the suspected pathophysiology. A combination of the inhibition of COX-1 in conjunction with an intrinsic regulatory defect in arachidonic-acid metabolism triggers a biochemical cascade involving the generation of leukotrienes and the release of mast-cell and eosinophil-derived mediators.

Ibuprofen is a safe alternative antipyretic, in children with a history of reactions to paracetamol as the molecular structure is quite dissimilar. All children with a suspected NSAIDs hypersensitivity reaction should be challenged and re-challenged periodically. COX2-specific medications, although generally not approved in children, have been prescribed and are useful as alternative medications. COX2-specific medications are the best option for all NSAID hypersensitive children. In children with NSAIDs hypersensitivity, a COX2-specific medication can be prescribed without a prior drug provocation test (6). Algorithm for the management of children with non-steroidal anti-inflammatory drugs hypersensitivity reactions has been proposed (6). In case of a confirmed hypersensitivity reaction to a single drug it is possible to use an alternative NSAID even if off label. If is present a cross-intolerance is possible a) use confirmed alternatives NSAID even if off label, b) use alternative drugs, c) use a desensitization in selective cases (6).

Perioperative drugs

Dewachter et al (7) reported an overall incidence for perioperative anaphylaxis in the pediatric population of one in 7741 anesthetic procedures. Rates appear to be higher in selected populations, as in children with congenital malformations, submitted to several interventions (8). In contrast to adults, neuromuscular blocking agents are less commonly incriminated in children, with an estimated incidence at one in 80 000 anesthetic procedures being the second leading cause after latex in this setting (9). Anaphylaxis due to induction agents is rare. Brockow et al recommended drug concentration for skin testing aiming to achieve a specificity of at least 95%. It has been possible to recommend specific drug concentration for perioperative drugs, heparins, platinum salts and radio contrast media (10) (Table 4). For the management of perioperative drug allergy it is necessary to carry out clinical history suggestive for DHR, in vivo and in vitro tests (if available), research of an alternative product, always through in vivo and in vitro tests, possible use of the responsible drug through a desensitization scheme.

Radio contrast media

The overall reported incidence of immediate reactions to intravenous nonionic iodinated radio contrast media in children is lower than in the adult population.

DHR with severe cardiovascular or respiratory involvement has been reported with an incidence of 0.07% for nonionic contrast media in children aged 1–19 years (11). Gadolinium-containing contrast media were associated with DH reactions in 0.04% of the pediatric patients (12-13).

Table 4. Nonirritating test concentrations for main perioperative drugs and selected other drugs

Drug		Skin prick test		Intradermal test	
Generic name	Undiluted Concentration (mg/ml)	Dilution	Maximum concentration (mg/ml)	Dilution	Maximum concentration (mg/ml)
Atracurium	10	1/10	1	1/1000	0.01
Cis-atracurium	2	undiluted	2	1/100	0.02
Etomidate	2	undiluted	2	1/10	0.2
Fentanyl	0.05	undiluted	0.05	1/10	0.005
Propofol	10	undiluted	10	1/10	1
Thiopental	25	undiluted	25	1/10	2.5
Ketamine	10	undiluted	10	1/10	1
Midazolam	5	undiluted	5	1/10	0.5
Sufentanil	0.005	undiluted	0.005	1/10	0.0005
Morphine	10	1/10	1	1/1000	0.01
Mivacurium	2	1/10	0.2	1/1000	0.002
Rocuronium	10	undiluted	10	1/200	0.05
Vecuronium	4	undiluted	4	1/10	0.4
Suxamethonium	50	1/5	10	1/500	0
Carboplatin			10 mg/ml		1 mg/ml
Oxaliplatin			1 mg/ml		0.1 mg/ml
Cisplatin			1 mg/ml		0.1 mg/ml
Adalimumab			50 mg/ml		50 mg/ml
Etanercept			25 mg/ml		5 mg/ml
Infliximab			10 mg/ml		10 mg/ml
Omalizumab			1.25 mcg/ml		1.25 mcg/ml
Chlorhexedine			5 mg/ml		0.002 mg/ml

Chemotherapeutics drugs

Carboplatin and asparaginase are frequent causes of DH among treated children. In one review on children affected by low-grade glioma, 44 of 105 children (42%) developed hypersensitivity to carboplatin (14). Seventeen (9.2%) of the 185 children, affected by different solid tumors and treated with etoposide–carboplatin, presented an allergic reaction to carboplatin: 2% at 6 courses, 11% at 12 courses, and 47% at more than 12 courses (15).

Hypersensitivity reactions to asparaginase have been reported in up to 40% of the treated children (16-17).

It is useful, in case of suspected allergy to Radio contrast media and Chemotherapeutics drugs, follow the same indications given in case of suspected allergy to perioperative drugs.

Conclusions

DHRs in children have a parent-reported prevalence of around 10%, with a much lower real prevalence, and a lower prevalence of confirmed DHRs as compared to adults (5).

Beta lactams (BLs)are the main drugs implicated in DHRs among children and the most common cause of concern. Nonsteroidal anti-inflammatory drugs, non-BL antibiotics, perioperative drugs, anesthetics, radio contrast media, and cytotoxic drugs are also frequently suspected. The most common reactions are nonimmediate maculopapular exanthema and urticaria. Drugs are the third identified cause for anaphylaxis among children. Facial swelling associated with NSAID hypersensitivity appears to be quite specific for children. The diagnostic approach to DHR diagnosis is based on experience in adults, but its adequacy in children has to be further evaluated. For example, drug provocation test without previous skin tests can be considered in children with non-severe maculopapular and nonimmediate urticarial exanthemas (5). Furthermore, there is higher evidence to recommend skin tests in children with suspected drug hypersensitivity to anticonvulsants, chlorhexidine (specific IgE determinations are available and recommended), heparins, neuromuscular blocking agents (specific IgE determinations are available and recommended), platinum salts, radiocontrast media, blue dyes, proton pump inhibitors (5).

Conflict of interest: None to declare

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