Hypersensitivity reactions to NSAIDs in children

Reacții de hipersensibilitate la AINS la copii

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Abstract

Acetylsalicylic acid and other nonsteroidal anti-inflammatory drugs (NSAIDs) are a group of medications commonly used in adults and children. Hypersensitivity reactions to NSAIDs are unpredictable reactions that occurr in susceptible individuals. In accordance with EAACI/WAO reccomendations, depending on underlying mechanisms, hypersensitivity reactions to NSAIDS can be classified as allergic if they are immunologically mediated or nonallergic if the mechanism is a nonimmune one. In the paediatric population, betalactam antibiotics are the most common hypersensitivity reactions triggers followed by NSAIDs and non-betalactam antibiotics. Viral infections, atopy, asthma, and chronic urticaria were reported to be significant risk factors for reactions to NSAIDs in children. There are several protocols and tools for guiding allergists to perform a correct diagnosis and a complete allergy work up in patients presenting with a suspected hypersensitivity reaction to NSAID, in order to provide a safe therapeutic alternative.

Keywords: *acetylsalicylic acid, NSAID, hypersensitivity, asthma, urticaria, children*

Rezumat

Acidul acetilsalicilic și alte antiinflamatoare nesteroidiene (AINS) reprezintă un grup de medicamente frecvent utilizate la adulți și copii. Reacțiile de hipersensibilitate la AINS sunt reacții imprevizibile ce apar la subiecți predispuși. Conform recomandărilor EAACI/OMS, în funcție de mecanismul subiacent, reacțiile de hipersensibilitate la AINS sunt clasificate în reacții alergice dacă sunt mediate imun, respectiv non-alergice dacă mecanismul este unul non-imun. În populația pediatrică, antibioticele din clasa betalactamine reprezintă cea mai frecventă cauză de reacție de hipersensibilitate, urmate de AINS și antibiotice non-betalactamice. Infecțiile virale, atopia, astmul și urticaria cronică au fost raportate drept factori semnificativi de risc pentru reactivitatea la AINS la copii. Există câteva protocoale și instrumente la îndemâna alergologului pentru a putea stabili diagnosticul corect la pacientul cu suspiciune de reacție de hipersensibilitate la AINS, pentru a putea asigura o alternativă terapeutică sigură.

Cuvinte-cheie: *acid acetilsalicilic, AINS, hipersensibilitate, astm, urticarie, copii*

Introduction

Acetylsalicylic acid and other nonsteroidal anti-inflammatory drugs (NSAIDs) are a group of medications with heterogenic chemical structures, able to inhibit with various degrees of specificity and efficacy the cyclooxygenase (COX) enzymes responsible for the prostaglandin synthetase pathway of arachidonic acid metabolism[1].

Hypersensitivity reactions to NSAIDs are unpredictable reactions that occurr in susceptible individuals, defined by the World Health Organization (WHO) as type B reactions[2], and should be clearly differentiated from type A reactions, predictable, based on pharmacological mechanisms and occurring in all individuals if a sufficient dose is used. In accordance with EAACI/WAO reccomendations, depending on underlying mechanisms, hypersensitivity reactions to NSAIDS can be classified as allergic if they are immunologically mediated, or nonallergic if the mechanism is a nonimmune one[3].

NSAIDs have been reported to be the second most common cause of drug hypersensitivity reactions after betalactam antibiotics, but according to some recent studies, they have risen to the most common cause. The prevalence of hypersensitivity to NSAIDs among adult asthmatic patients assessed by questionnaires or medical records is ranging from 4.3% to 11%[4] and can be as high as 21% if diagnosis includes provocation tests[5]. Among patients with bronchial asthma and nasal polyps, the prevalence of ASA hypersensitivity may reach 25.6%[6]. In the pediatric population, betalactam (BL) antibiotics are the most commonly involved drug group, followed by nonsteroidal anti-inflammatory drugs (NSAIDs) and non-betalactam antibiotics[7]. All NSAIDs can induce a hypersensitivity reaction, regardless of the chemical structure or anti-inflammatory potency[8].

There are evidence showing that young children are at higher risk for adverse drug reactions than older children[7], and that underlying viral infections may act as cofactors in susceptible individuals[9]. Also, atopy, asthma, and chronic urticaria were reported to be significant risk factors for reactions to NSAIDs in children[7,10].

Cutaneous and respiratory reactions are the most common manifestations of adverse reactions to NSAIDs in children. In a study enrolling more than 27000 children less than 2-years-old, treated with ibuprofen and paracetamol for an acute febrile illness, there were no registered cases of acute anaphylaxis[11] .

There are data showing that the heteroaryl acetic acid group of NSAIDs (like naproxen, diclofenac, ibuprofen) carry a higher risk of anaphylactic reactions than other groups[12], while pyrazolones are the most likely NSAIDs to induce immediate hypersensitivity reactions[13]. COX-2 selective inhibitors have a much lower risk to induce hypersensitivity reactions, estimated at 0.008% incidence[14] .

Definitions of types of NSAIDs hypersensitivity[8]:

Nonimmunologically mediated (cross-reactive) hypersensitivity reactions to NSAIDs

NSAIDs-exacerbated respiratory disease: hypersensitiv-

Table 2 The classification of NSAIDs according to the chemical structure[8]

Salicylic acid derivates	Aspirin (acetylsalicylic acid) Sodium salicylate Salsalate Diflunisal Salsalate Sulfasalazine
Para-aminophenol	Acetaminophen (paracetamol)
Propionic acid derivates	Ibuprofen Naproxen Fenoprofen Flurbiprofen Ketoprofen Oxaprozin
Acetic acid derivatives	Diclofenac Etodolac Ketorolac Indomethacin Sulindac Tolmetin Nabumetone
Enolic acid derivatives	Pyrazolones: Phenylbutazone, Dipirone Oxicams: Piroxicam, Meloxicam, Tenoxicam, Lornoxicam
Fenamic acid derivatives (Fenamates)	Mefenamic acid Meclofenamic acid Flufenamic acid Tolfenamic acid
Selective COX-2 inhibitors (Coxibs)	Celecoxib Etoricoxib

ity reactions induced by acetylsalicylic acid or other NSAIDs, manifesting primarily as bronchial obstruction, dyspnea, and nasal congestion/rhinorrhea, occurring in patients with an underlying chronic airway respiratory disease (asthma/ rhinosinusitis/ nasal polyps).

NSAIDs-exacerbated cutaneous disease: hypersensitivity reactions induced by acetylsalicylic acid or other NSAIDs manifesting as wheals and/or angioedema occurring in patients with a history of chronic spontaneous urticaria.

NSAIDs-induced urticaria/ angioedema (NIUA): hypersensitivity reactions induced by acetylsalicylic acid or other NSAIDs manifesting as wheals and/or angioedema occurring in otherwise healthy subjects (without history of chronic spontaneous urticaria).

Immunologically mediated (noncross-reactive) hypersensitivity reactions to NSAIDs

Single NSAID-induced urticaria/angioedema or anaphylaxis (SNIUAA): immediate hypersensitivity reactions to a single NSAID or to several NSAIDs belonging to the same chemical group, manifesting as urticaria, angioedema and/ or anaphylaxis.

Single NSAID-induced delayed hypersensitivity reactions (SNIRD): hypersensitivity reactions to a single NSAID, appearing usually within 24-48 hours after the drug administration and manifesting by either skin symptoms (exanthema, fixed drug eruption), other organ-specific symptoms (e.g., renal, pulmonary), or severe cutaneous adverse reactions.

NSAID-induced rhinitis/asthma – aspirin-exacerbated respiratory disease (AERD) in children

The association between asthma, nasal polyposis or chronic rhinosinusitis and aspirin/NSAIDs hypersensitivity reaction was known over the years as Samter's triad, Widal's syndrome, aspirin-induced asthma, aspirin intolerant asthma or aspirin-sensitive rhinosinusitis/ asthma syndrome[15]. The actual term proposed for this clinical entity is aspirin-exacerbated respiratory disease (AERD), referring to the pathogenic characteristics of this particular type of asthma, only occasionally agravated by aspirin/ NSAIDs[16] .

In preschool children, the ibuprofen, a nonspecific inhibitor of COX-1 (mainly) and COX-2, is extensively used for fever and acute pain management[17].

Acetaminophen is the most ubiquitously used antipyretic medication, with no significant effect on peripheral COX-1 and COX-2, acting in fact on COX-3, enzyme found in brain and spinal cord. The selective inhibition of COX-3 mediates the pain and fever relieving, without unwanted gastrointestinal side effects[18]. Aspirin (ASA) hypersensitivity, investigated by standardized challenge tests, was estimated to be between 0 and 28% in children with asthma, most of them being older than 6 years of age[1], and 2% in young atopic children attending a general allergy clinic[19]. It was noted that AERD in childhood has much more favorable clinical characteristics and course than in adulthood, the asthma outcome is described to be milder and is well controlled in the short-term follow-up[20] .

The mechanism of hypersensitivity to ASA and other NSAIDs in asthmatic patients is considered to appear due to capability of the drugs to inhibit cyclooxygenase 1 (COX-1), an enzyme that metabolizes arachidonic acid to prostaglandins, thromboxanes and prostacyclin[21]. The abnormal function of leukotriene pathway of arachidonic acid metabolism that involves a basal increased synthesis of cysteinil-leukotrienes, exacerbated by PGE2 inhibition secondary to aspirin/ NSAIDs ingestion, has been postulated by multiple investigators as mechanism, and leukotriene receptor antagonists seem to be effective in the treatment of AERD[8]. Several genetic polymorphisms (most related to AA metabolism pathway enzymes) have been associated with AERD.

Cutaneous hypersensitivity to NSAIDs in children

Chronic urticaria is generally an uncommon disease in children, epidemiologic studies reporting that up to 3% of the population might be affected[22]. However, NSAID hypersensitivity exists in patients with chronic spontaneous urticaria younger than 12 years of age[23]. The most common clinical manifestation of NSAID hypersensitivity in preschool children is facial angioedema with or without generalized urticaria. The possible mechanism of urticaria exacerbation is similar as in AERD, the inhibition of COX-1. There are reported cases of probably immune-mediated episodes of urticaria and/or angioedema induced by a specific NSAID, or cases of delayed-type hypersensitivity reactions, like fixed drug eruptions and toxic epidermal necrolysis[24].

Diagnostic approach to drug hypersensitivity in children

The diagnosis relies on a complete allergy work up, ideally performed 1 to 6 months after the complete recovery after the initial reaction. The diagnostic methods for paediatric patients are the same as for adults, and consist of precise clinical history, skin tests, laboratory tests (if available and validated), and drug provocation tests.

Provocation tests, the gold standard for the diagnosis of NSAID hypersensitivity, should respect the general principles of safety and benefit to the patient[25]. They are particularly important in children, as the main culprits (i.e., ibuprofen and paracetamol) will often be needed again in future treatments, and in many cases delayed reactions cannot be excluded by other tests.

Oral and inhalation challenge protocols are published. For nonasthmatic children with angioedema/urticaria or mixed-type reactions, a single challenge dose of 100 mg of ibuprofen or aspirin and 180 mg of acetaminophen have been reccomended for children more than 8 years of age[26].

Another exemple of protocol for children, taking into considerations the weight variations, suggest using 2.5 mg/kg of body weight of either aspirin or ibuprofen or 5 mg/kg of acetaminophen ingested at hourly intervals to a maximal dose of 10 mg/kg and 20 mg/kg, respectively, or until a positive reaction is elicited[1]. A firm diagnosis of NSAID hypersensitivity in children is required as most of specific COX-2 inhibitors used as alternatives in adults are not approved for paediatric use and have no liquid formulations[8].

Management

As with any kind of allergic reactions, the best approach to management is the avoidance of re-exposure. This would be easy if there were reasonable alternatives. Unfortunately, the most common clinical presentation of NSAIDs hypersensitivity in children seems to be of the nonspecific cross-reactive type, with immediate angioedema/urticaria of unpredictable severity. There was described a cross-reactivity to acetaminophen in young children with hypersensitivity to ibuprofen, estimated by various investigators to be between 4% and 25%[27,28,29].

Conclusions

During childhood, everyone is exposed at least once to a NSAID. Hypersensitivity reactions in children are an important issue because there are no alternatives, on a routine base, to treat fever and/or pain. Atopy and infections are the most important risk factors to consider especially regarding reactions to NSAIDs. There are several protocols and tools to guide allergists to perform a correct diagnosis and a complete allergy work up in patients presenting with a suspected hypersensitivity reaction to NSAID. The diagnostic process should result in providing the patient with written information both on forbidden and on alternative drugs or therapeutic solutions. ■

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