Hypersensitivity to Nonsteroidal Anti-inflammatory Drugs in Children and Adolescents: Cross-Intolerance Reactions

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Abstract

Nonsteroidal anti-inflammatory drugs (NSAIDs) are used worldwide and are responsible for several types of drug hypersensitivity reactions (DHRs) in all age groups. The 2 major groups of DHRs to NSAIDs are those induced by immunological mechanisms (selective reactions) and those where inflammatory mediators are released through activation of the prostaglandin-leukotriene pathway without specific immunological recognition (cross-intolerance). In the present review, we focus on cross-intolerance reactions, which are the most frequent DHRs and are becoming a topic of major interest in children and adolescents.

Paracetamol and ibuprofen are the drugs that most frequently cause DHRs in children; other NSAIDs are responsible for reactions in adolescents. In vivo and in vitro tests are of limited diagnostic value, with some exceptions for the less common selective reactions. In cross-intolerance, the clinical history and controlled administration are in many instances the only way to establish a diagnosis and look for alternatives. The clinical history is diagnostic when consistent symptoms occur repeatedly after exposure to NSAIDs with different chemical structures.

Cutaneous and respiratory symptoms often co-occur in young children. The natural history of these reactions in children is unknown, and some patients can develop tolerance over time. Atopy remains a major risk factor for cross-intolerant reactions. The increasing interest in hypersensitivity to NSAIDs with improvements in patient phenotyping and the information provided by pharmacogenetics will improve our understanding and management of these reactions in the near future.

Key words: Hypersensitivity drug reactions. NSAIDs, cross-intolerance. Cysteinyl leukotrienes. NSAID-exacerbated respiratory disease. NSAID-exacerbated cutaneous disease. NSAID-induced urticaria/angioedema.

Resumen

Los antiinflamatorios no esteroideos (AINEs) son ampliamente utilizados en todo el mundo y en todos los tramos de edad. Son responsables de un número importante de reacciones de hipersensibilidad a fármacos (RHFs), que no sólo afectan a adultos sino también a niños y adolescentes. Existen dos grandes grupos: reacciones selectivas, inducidas por mecanismos inmunológicos específicos, y de intolerancia cruzada (IC), donde se liberan mediadores inflamatorios en ausencia de reconocimiento inmunológico específico. En esta revisión nos ocuparemos de la IC, que es la causa más frecuente de RHFs y resulta de gran interés en niños y adolescentes.

El paracetamol y el ibuprofeno son los medicamentos más frecuentemente implicados en las RHFs en niños. El uso diagnóstico de los tests *in vivo* e *in vitro* es muy limitado, con algunas excepciones en las reacciones selectivas. En las de IC, la historia clínica y la administración

controlada son en ocasiones la única vía para confirmar el diagnóstico y determinar las alternativas terapéuticas más adecuadas. La historia clínica tiene valor diagnóstico cuando se reproducen síntomas consistentes repetidamente tras la exposición a AINEs no relacionados estructuralmente.
En niños de corta edad es especialmente frecuente la combinación de síntomas cutáneos y respiratorios. Aunque se desconoce la historia natural de la IC en niños, es probable que se desarrolle tolerancia a lo largo de la vida.
El fenotipado detallado junto con la información proporcionada por la fármaco-genética no sólo proporcionarán un conocimiento más preciso de la IC sino que también facilitará el manejo clínico de estos pacientes.

Palabras clave: Reacciones de hipersensibilidad a fármacos. AINEs. Intolerancia cruzada. Cisteinil-leucotrienos. Enfermedad respiratoria exacerbada por AINEs. Enfermedad cutánea exacerbada por AINEs. Urticaria/angioedema inducidos por AINEs.

Introduction

Nonsteroidal anti-inflammatory drugs (NSAIDs) are among the most highly consumed drugs worldwide for all age groups [1,2]. They are used to treat pain, fever, and various inflammatory diseases [3]. Despite their beneficial effects, they can induce adverse drug reactions (ADRs) [1]. Some ADRs are dose-dependent (Type A), but others occur at therapeutic or even at low, nontherapeutic concentrations (Type B) [4]. The latter include drug hypersensitivity reactions (DHRs) [5]. Although originally reported in adults, it soon became clear that DHRs can also occur in children and adolescents [6,7].

NSAIDs, particularly paracetamol and ibuprofen, are commonly prescribed to children, among whom they have proven to be relatively safe, despite their widespread consumption [8-10]. Studies assessing the risk of serious ADRs due to ibuprofen in more than 80 000 febrile children reported only 795 hospital admissions [11,12]. Another study of 1879 febrile children with asthma showed that short-term use of ibuprofen can reduce asthma morbidity [13]. However, ibuprofen and paracetamol have recently been included in a list of 20 medications thought to be responsible for ADRs in children and adolescents [14].

This review deals specifically with DHRs to NSAIDs in children and adolescents. The many initiatives that have updated our understanding of these reactions in adults include a position statement on clinical entities [15], a new nomenclature for classification [16], and guidelines for advanced phenotyping [17]. Hypersensitivity to NSAIDs in children, however, has received much less attention [6,18].

Classification of DHRs to NSAIDs

As stated above, NSAIDs are widely consumed by patients of all ages [2,8-10] and responsible for at least 25% of all ADRs, including DHRs [5].

DHRs to NSAIDs can be caused by specific immunological mechanisms (allergic reactions) or by biochemical processes linked to arachidonic acid metabolism (nonallergic hypersensitivity or cross-intolerance [CI] reactions) [16]. Reactions induced by CI are frequent in all age groups, including children and adolescents [18,19]. DHRs to NSAIDs have more potential underlying mechanisms than DHRs to ß-lactam antibiotics, which result from specific IgE or T-cell responses [20]. For example, NSAIDs-induced urticaria could

Table. Classification of Hypersensitivity Reactions to Nonsteroidal Anti-inflammatory Drugs

	Type of reaction	Clinical manifestations	Timing of the reaction	Underlying disease	Mechanism
Cross intolerance (nonallergic)	*NSAID-exacerbated respiratory disease (NERD)*	Bronchial obstruction, dyspnea and/or nasal congestion/rhinorrhea	Acute (immediate to several hours after exposure)	Asthma Rhinosinusitis	COX-1 inhibition
	NSAID-exacerbated cutaneous disease (NECD)	Wheals and/or angioedema		Chronic urticaria	COX-1 inhibition
	NSAID-induced urticaria/angioedema (NIUA)	Wheals and/or angioedema			Unknown, probably COX-1 inhibition
	Single-NSAID-induced urticaria/anaphylasis (SNIUAA)	Wheals/angioedema/anaphylaxis			IgE-mediated
Selective response (allergic)	*Single-NSAID-induced delayed reactions (SNIDR)*		Delayed onset (usually more than 24 hours after exposure)		T cell–mediated
		Maculopapular exathema			
		Fixed drug eruption			
		Acute generalized exanthematous pustulosis			
		Drug reaction with eosinophilia and systemic symptoms			
		Stevens-Johnson syndrome/Toxic epidermal necrolysis			
		Organ-specific reactions			

be due to an IgE-dependent mechanism, a T-cell response, or CI [16]. Although some entities induced by CI occur in both adults and children [5,19], others, such as facial and lip angioedema, are more common in children [21,22].

According to the European Academy of Allergy and Clinical Immunology (EAACI) [16] the major entities induced by CI [Table] are as follows:

1. NSAIDs-exacerbated respiratory disease (NERD), which is observed in patients with underlying chronic respiratory disease (asthma/rhinosinusitis/nasal polyposis) aggravated by intake of NSAIDs. This condition was previously known as aspirin (ASA)-exacerbated respiratory disease (AERD), ASA-induced asthma (AIA), or the ASA triad.
2. NSAIDs-exacerbated cutaneous disease (NECD), which is observed in patients with a previous history of chronic spontaneous urticaria (CSU) aggravated by intake of NSAIDs.
3. NSAIDs-induced urticaria/angioedema (NIUA), in which patients develop symptoms following intake of NSAIDs in the absence of CSU.

CI reactions were previously known as idiosyncratic or pseudoallergic reactions [23]. The term cross-reactive should be reserved for reactions induced by specific immunological mechanisms, although many authors still use it [16]. Strong COX-1 inhibitors are usually responsible for CI, although weak COX-1 inhibitors and even selective COX-2 inhibitors can trigger CI [24]. The term *blended reaction* refers to CI with respiratory and cutaneous involvement [23], which can also affect children and adolescents following intake of NSAIDs [6,18].

Children and adolescents can be affected by any of the above-mentioned entities. However, the specific features associated with younger age groups include the type, severity, and frequency of the reaction and the drug involved [18,25].

Epidemiology

Although original epidemiological studies are somewhat scarce, several manuscripts deal with the prevalence of ADRs to NSAIDs [26-28], including DHRs [29,30], and some analyze DHRs to NSAIDs in the context of total ADRs [31-33]. Studies can also be based on spontaneous reporting [31], where the description of the entities and drug involvement are assigned by probability [34], without considering the specific mechanism (CI or selective reaction) [23,35].

Other studies examine specific conditions such as angioedema in children [22], angioedema plus urticaria [36], respiratory symptoms [37], and both skin and respiratory involvement [38]. However, most studies use mixed populations of adolescents and adults [29,39,40], and we must determine the exact percentage of children/adolescents before drawing conclusions. Some studies include patients aged ≥14 years [29]; few studies include children aged <12 years and even fewer include children aged <5 years [19,41]. Variability in study design also affects interpretation [42].

Studies from the 1970s and 1980s were neither sufficiently detailed nor supported by laboratory data [18,43] or used imputability criteria that prevented a definitive diagnosis from being established [34,44]. In general, detailed allergological studies are scarce for both children and adults [18,45], although sufficient information is available to estimate the relevance of DHRs in children.

A recent study of 659 NSAID-hypersensitive adolescent/adult patients found that 76% had CI [29]. A retrospective study showed that antibiotics and NSAIDs were the most common triggers of DHRs [46]. As this study grouped all antibiotics together, we can infer that NSAIDs were the main culprits. A cross-sectional study in which 1015 patients were evaluated based on self-reported replies to a questionnaire showed that NSAIDs were the main cause of DHRs, followed by ß-lactams and sulfonamides [47].

In a recent study of the largest series of DHRs to date, we confirmed that in 1682 of 4400 initial patients, NSAIDs were the culprit drugs in 47% of cases and ß-lactam antibiotics in less than 20% [30]. Within NSAIDs, no differences in reaction patterns were found between adolescents and adults [30], a result that is consistent with that of previous studies [40].

NSAIDs were the main culprit drugs in another study of patients aged <18 years with anaphylaxis [48]. Moreover, in a large cohort of children with anaphylaxis, most culprit drugs were NSAIDs, mainly ibuprofen [49].

Studies of DHRs in children do not usually assess the underlying mechanism, whose patterns of reactions may differ from those of adults [42]. Another study evaluating 3275 confirmed cases, of which 10% were children and 22% adolescents, found significant differences in the frequency of exanthematic reactions at younger ages [50].

The prevalence of NERD in adults ranges from 4.3% to 10.9% [51-53], although data are scarcer for children. In an early study, 28% of children with chronic asthma were intolerant to ASA [54]; however, another study found that oral administration of ASA did not lead to a significant effect on respiratory function [55].

Some studies have focused on the etiology and natural history of CSU in children, although none have assessed intolerance to NSAIDs [56-59].

NIUA was shown to account for 61% of patients with CI [29]. CI accounted for 47% of all DHRs followed by allergy to ß-lactams [30]. NSAIDs frequently elicit isolated angioedema in children [60], as reported, occurring in more than 85% of children with CI after challenge [19].

Blended reactions must be differentiated from anaphylaxis in selective responses. They occur in 9%-40% of NSAID-induced reactions, ie, more frequently than NERD [29,36]. One study reported that blended reactions occur in 9.7% of children [61]. In a study of children aged 9-14 years, 14% of CI episodes following a drug provocation test (DPT) were blended reactions, in which the patients presented angioedema with asthma and/or rhinoconjunctivitis [73]. The reaction elicited (blended or respiratory) in children with CI varied with the provocation protocol used, as well as with the patient's age and genetic background. More paracetamol-induced reactions were observed in Asian children with early onset of CI, as was a lower incidence of respiratory symptoms upon challenge in younger patients [62].

Drugs Involved

All NSAIDs, including strong and weak COX-1 and selective COX-2 inhibitors, can induce CI [18,35] in all age groups [7,18]. NSAIDs are increasingly used in both children and adults owing to higher demand and the introduction of new compounds [7]. In addition to ibuprofen and paracetamol, consumption of aspirin, naproxen, indomethacin, and COX-2 inhibitors (at older ages) has increased [7].

Shortly after the first description of AIA, reactions to other NSAIDs were also described [63,64]. All strong COX-1 inhibitors can induce the same effects as ASA [35,65]. Interestingly, the first adult cases reported were considered "intrinsic asthmatics," although the first pediatric cases were atopic [37,66,67].

Ibuprofen and paracetamol have been implicated in anaphylaxis in children, although the underlying mechanism was not assessed [49]. DHRs to paracetamol are frequent in patients with ibuprofen-induced anaphylaxis [36.8%], whereas a previous reaction to ibuprofen was reported in only a fifth of patients with paracetamol-induced anaphylaxis [49]. However, as with all DHRs, an oral DPT is frequently needed for diagnosis, as demonstrated by a study where DPT confirmed paracetamol hypersensitivity in only 4% of children [68].

Ibuprofen caused bronchospasm in a 17-year-old boy with AIA [69]. ASA, which is taken less frequently at younger ages, has been implicated in the development of urticaria and/or angioedema in atopic children [63] and in a child with a positive oral challenge result to paracetamol [68]. ASA has also been shown to worsen respiratory function in asthmatic children aged between 7 and 14 years [55].

As for NECD, adolescent data [70] indicate that patients with CSU might also experience exacerbations after intake of NSAIDs, particularly strong COX-1 inhibitors [61].

All NSAIDs including weak COX-1 and selective COX-2 inhibitors have been implicated in NIUA in adults and adolescents [24,29] and children [18]. Paracetamol and ibuprofen are the analgesics that most frequently induce DHRs in children. Paracetamol was the culprit drug in 5.5% of children [71], and up to 25% of children with CI showed a positive response to this drug [36,61,68,72]. However, the response to paracetamol can depend on age and other factors [62]. Anecdotal information suggests that hypersensitivity to paracetamol can resolve over time and that patients with positive challenge results at an early age may tolerate the drug years later. Therefore, assessment of hypersensitivity using DPT years after the incident could underestimate the true prevalence of the problem in children.

Blended reactions are common in children and have been reported for ibuprofen and other drugs [36].

Clinical Characteristics and Pathophysiology

NERD

NERD comprises a heterogeneous set of syndromes that involve the upper and/or lower airways. The ASA triad as initially described (asthma, rhinitis/nasal polyposis, and ASA intolerance) is not fully expressed in children and adolescents but instead involves the upper/lower airways to varying degrees [18]. Asthma and nasal polyposis are extremely rare in children, although they have been reported [73,74]. Asthma and/or rhinitis induced by NSAIDs is more common [75].

Contrary to the first descriptions of AIA, where most patients were adults with a negative skin test result (diagnosed with "intrinsic asthma"), most children/adolescents with NERD are atopic, with positive skin test results to inhalant allergens, particularly house dust mites [18]. These patients usually develop mild airway symptoms with or without ocular involvement [76].

The exacerbation of asthma attacks and other respiratory manifestations is attributed to COX-1 inhibition, which shunts the arachidonic acid pathway from prostaglandins (PG) towards synthesis of cysteinyl leukotrienes (CysLTs) during inflammation. The degree of COX-1 inhibition differs according to the NSAID involved and correlates with its capacity to induce bronchospasm [65]. Inflammatory mediators, including LTC_4, LTD_4, and hydroxyeicosatetraenoic acids, also participate in the regulation of mucus glycoprotein secretion, which has a role in NSAIDs-induced asthma attacks [77]. An eicosanoid imbalance in children with NERD was recently reported [73].

An alternative hypothesis is that suppression of PGE2 in chronic viral infection induces lymphocytes to attack target cells in the respiratory tract [78]. Interestingly, meclofenamate can induce asthma in adolescent girls during the follicular phase of the menstrual cycle, probably as a consequence of monthly variations in serum $PGF_{2\alpha}$ [79]. Although this finding is common, no comprehensive detailed studies have been carried out.

NECD

Around 30% of patients with CSU experience a worsening of their symptoms after taking strong COX-1 inhibitors [80]. Although CSU is rare in children [81], it does occur [82-85] and can be exacerbated by NSAIDs, particularly strong COX-1 inhibitors [38]. A severe anaphylactic reaction to ibuprofen in a child with CSU and NSAID hypersensitivity has been described [38]. Reports are often insufficiently detailed to enable a precise, unequivocal diagnosis to be established [45].

Patients with NECD show increased N-methylhistamine metabolites and CysLT levels in urine [86,87]. The complex interaction of factors underlying CSU and NECD includes autoimmune diseases, allergens, infections, physical factors, and other as yet unidentified triggers that are also relevant in children [88].

NIUA

NIUA is the most common type of NSAID-induced DHR for all age groups [29,30], including children [19]. The most frequent clinical condition is facial angioedema followed by generalized urticaria [36], although both urticaria and angioedema can appear simultaneously [19], especially in atopic children [63].

Clinical entities are not always fully described, and despite suggestive symptoms, NIUA can sometimes only be putatively inferred. Anaphylaxis may also be induced by CI and must

be differentiated from selective responses [29]. Clinically, severe responses including skin and respiratory symptoms (ie, blended reactions) may be considered anaphylactic according to recent guidelines of the World Allergy Organization [89]. However, most NIUA reactions, even when severe, are not associated with an early drop in blood pressure. Likewise, although abdominal pain or discomfort may be part of a severe reaction, vomiting and diarrhea are rarely reported in children [36,38,62].

Whilst similarities have been found between the mechanisms underlying NECD and NERD [87], to our knowledge, no such data have been reported for NIUA. Preliminary evidence suggests that NIUA and NERD present different urinary eicosanoid profiles [90].

Nonpruriginous isolated angioedema, which often affects the face and other soft tissues, can be caused by NSAIDs [29,30,91,92]. The mediators involved remain unknown, although it is tempting to speculate on the participation of other mechanisms such as the bradykinin pathway [93].

Blended reactions

Blended reactions can be caused by high doses of ASA, leading to local release of histamine and CysLTs and causing vasoactive effects outside the lung. Pediatricians frequently deal with this type of reaction [19,71,94].

NSAIDs and Food Allergy Reactions

Food allergy has a prevalence of 7%-8% in children, with fruits, milk, and vegetables accounting for two-thirds of reactions [95]. Lipid transfer proteins, which are present in many fruits and nuts [96-98], are major triggers in children and adolescents, as are seafood and mite-contaminated food [99]. Ingestion of food allergens alongside NSAIDs (usually strong COX-1 inhibitors) can trigger anaphylaxis and urticaria/angioedema [99-101]. Physical exercise is often required as a cofactor [102,103]. In a typical scenario, a patient sensitized to a food allergen (eg, peanut/peach), but with no clinical manifestations, takes a previously tolerated NSAID (commonly ibuprofen) and develops anaphylaxis from minutes to hours after intensive physical exercise [102].

Risk Factors

Risk factors for developing CI include a previous history of anaphylaxis, immediate and accelerated reactions, atopy, older age, and CSU [61].

In children and adolescents with NERD or NIUA, skin test positivity to inhalant allergens (eg, house dust mites, pollens, and allergens such as *Alternaria*) has been reported [19]. Doña et al [29] found that sensitization to house dust mite and grass and olive pollen can be a risk factor.

Other risk factors include the number of drugs taken and sex, with female adults at higher risk [104]. However, sex has not been shown to increase the risk for children [19]. Although atopy is more frequent in patients with AIA and patients with selective reactions to pyrazolones [67], this association was not found in a Spanish population [29]. Reduced use of ASA in favor of paracetamol in children could contribute to the increasing prevalence of asthma, atopic eczema, and allergic rhinitis in developed countries [105]. Atopy is also frequent in patients with NIUA, who were more likely to have high levels of specific IgE to *Dermatophagoides pteronyssinus* and *Blomia tropicalis* [106]. The association between *D pteronyssinus* and NIUA has also been reported in Spain [29].

Most studies of risk factors analyze the role of concomitant factors that are previous to or simultaneous with the drug (eg, food and exercise). NSAIDs can also influence the development and/or clinical course of rhinitis and asthma [107,108]. These cases do not involve hypersensitivity to NSAIDs but an interaction between NSAIDs and atopic status. The association between atopy, asthma, and NSAIDs is controversial, since it has been shown that short-term use of ibuprofen as anti-inflammatory medication in children can actually reduce the number of acute exacerbations [13].

The role of food allergy in the development of NECD or NIUA is controversial [70,80]. There is evidence that food allergy–induced anaphylaxis can occur after intake of ASA in patients with no previous history of DHRs to NSAIDs [109]. NSAIDs and/or exercise can facilitate absorption of allergens from the gastrointestinal tract [110], and ASA can induce mast cell activation leading to anaphylaxis, as seen in the skin prick test with the causative food allergen [111]. In our experience, adolescents with NIUA are not more sensitized to prevalent food allergens such as Pru p 3 or other lipid transfer proteins [112], although further studies are needed to confirm this observation.

Familial clustering has been observed in some types of hypersensitivity to NSAIDs, although a clear Mendelian pattern has not been found [113]. Most genetic studies of CI investigated NERD and polymorphisms in candidate genes [114], although 2 genome-wide association studies have been conducted [115,116]. Data are also available for NIUA [117,118], including a genome-wide association study that suggested a role for second messenger signaling pathways [119].

Diagnosis

DHRs to NSAIDs are incorrectly diagnosed more frequently than DHRs to other drugs [120]. The diagnosis of CI is based on a thorough clinical history, as diagnostic tests are of little value, in particular skin tests and the recently developed in vitro tests [104].

Clinical History

The expertise gained from NERD and NECD in adults is valuable for adolescents and children [15,16,121]. In NIUA, there is some disagreement as to whether the clinical history is valuable for diagnosis in adults/adolescents [104,122] and children [123].

In a large series of children with histories suggestive of DHRs, only 2.5% could be confirmed, and ibuprofen was the only culprit NSAID identified [124]. However,

details of whether the ibuprofen-induced reactions were CI or selective responses were not provided. In a retrospective study of patients with a history of hypersensitivity to NSAIDs, diagnosis was confirmed by challenge in only 8% of cases of asthma and 12% of cases of angioedema [125]. Oral challenge confirmed CI in 44% of patients in a study of children with a reaction suggestive of DHRs to NSAIDs [123].

The clinical history should include the sequence of events, symptoms, time between drug intake and the reaction, time between the reaction and the study, and the reason for administration [104]. We found that diagnosis of NIUA based on the clinical history was confirmed by challenge in 76% of cases. This percentage increased to 92% when more than 2 different NSAIDs were involved and the clinical history was clear [104]. However, there is some disagreement on this matter [122].

In Vitro Tests

A limited number of in vitro tests are available, although more research is needed to compare their efficacy [126].

The cellular allergen stimulation test, which quantitates basophil LT release, has been proposed for the diagnosis of AIA and can be extended to the other NERD entities (rhinitis and nasal polyposis) [127]. Initial studies showed promising results [128], which could not be confirmed in subsequent studies [129,130]. The basophil activation test has also been proposed [131], although its specificity is low [130,132].

In vitro assays for NECD are similar to those described for NERD but more difficult to apply and very unlikely to be used for children owing to the low prevalence of NECD in this group.

The use of the cellular allergen stimulation test and the basophil activation test to diagnose NIUA has been assessed [127]. Although there has been some success, several drawbacks remain [133]. The EAACI does not consider these techniques useful for diagnosis [16].

Drug Provocation Test

The principles used for DPT in children have been extrapolated from adults, except for the dose [5,16,18]. In many instances, the approach for evaluating hypersensitivity to NSAIDs is to assess tolerance rather than to identify the culprit drug [33]. We must also consider whether the alternative drug is a strong, weak, or selective COX-2 inhibitor. Since the reaction is expected with DPTs, low doses should be administered at regular intervals until the cumulative dose reaches the necessary therapeutic dose [36]. Furthermore, given that CI is the effect of an abnormal pharmacologic response, it is reasonable to increase the time between doses from the 30 minutes recommended for most challenges. Most published pediatric protocols use an interval of 60-90 minutes [28,50]. Some extremely sensitive patients may respond to lower doses than those usually recommended [134]. Guidelines for DPT have recently been published [135].

In NERD, DPT can be performed by nasal inhalation and bronchial or oral administration, with the latter considered the gold standard [135]. In adolescents aged 14-20 years, nasal inhalation (sensitivity of 80%-90%) is recommended [136]. If the result is negative, the bronchial provocation test can be considered. Bronchial provocation with lysine-ASA has long been used for the diagnosis of AIA and rhinitis in adolescents and adults, but less so in children [135].

Younger children should undergo oral DPT [61,63]. In one study, the NSAID was given incrementally every 20-30 minutes until the recommended dose was reached [125]. In a typical 25-kg patient, a proposed schedule for diagnosis of AIA is 25, 50, 100, and 250 mg every 30 minutes [137]. An alternative is to administer a constant dose at 1-hour intervals until the recommended therapeutic dose for age is reached [36,137]. According to this schedule, a therapeutic dose of 20 mg/kg for a 25-kg child is given as 4 doses of 125 mg at 1-hour intervals.

As stated above, NECD is uncommon in children. However, if younger patients with CSU must receive paracetamol or ibuprofen, a DPT should be performed to assess tolerance [38], as described below for NIUA.

In patients with NIUA, other drugs, such as paracetamol, tramadol, and selective COX-2 inhibitors, have been shown to exert little or no COX-1 inhibition [138]. Oral antihistamine has proven useful for preventing urticaria [138]. In otherwise healthy children with confirmed ibuprofen-induced NIUA, a DPT with paracetamol up to a cumulative dose of 15-20 mg/kg is imperative to enable safe antipyretic treatment as needed. In younger patients, most protocols use either equal or incremental doses at 1-hour intervals until the appropriate dose is reached [28,50]. In children with a positive result to a DPT with paracetamol or a convincing history of repeated reactions induced by paracetamol-containing formulations, the only alternative antipyretic would be off-label use of a specific COX–2 inhibitor. Although most such drugs are not indicated for fever or for children aged under 12 years, their safety has been proven in most patients in this age group [62,134].

Further Research

Childhood is the period during which we generally receive NSAIDs for the first time. As we grow older, the drugs taken in the first years of our lives may play a role in the development of future reactions and act as risk factors. Although data are available mainly for NERD and, to a lesser extent, NIUA, no well-defined genetic markers have been identified. The study of biological samples (urine, nasal and bronchoalveolar lavage fluid, saliva, and skin biopsy specimens) will be necessary to improve our understanding of the mechanisms involved in DHRs to NSAIDs and, subsequently, diagnosis of these reactions. Gene expression studies can also be useful for unraveling these mechanisms. Precise, advanced patient phenotyping [17] combined with molecular data will shed new light on our understanding of these diseases and thus facilitate patient management.

Concluding Remarks

NSAIDs are the drugs most commonly involved in DHRs in childhood [19]. They are frequently prescribed for the management of fever, pain, and other processes, and there are few alternatives, thus making understanding and management

of DHRs crucial for health care professionals. DHRs to NSAIDs are more complex than reactions to other drugs, such as ß-lactams, owing to the variety of triggering mechanisms (eg, IgE-dependent reactions, T-cell effector responses, and common CI-induced reactions). A precise diagnosis is often difficult owing to the limitations of in vitro and in vivo tests. Their complexity is demonstrated by the fact that exanthema-like reactions or urticaria, which are frequent in children and adults, may belong to any of these categories. We hope that this review will not only improve our understanding of DHRs to NSAIDs, but that it will also stimulate further studies of clinical and basic aspects of these diseases.

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Conflicts of Interest

The authors declare that they have no conflicts of interest.

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