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

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Abstract

Nonsteroidal anti-inflammatory drugs (NSAIDs) are used throughout the world to treat pain and inflammation; however, they can trigger several types of drug hypersensitivity reactions (DHRs) in all age groups. Although most such reactions occur through activation of the leukotriene pathway without specific immunological recognition (cross-intolerance), a significant number of DHRs to NSAIDs are due to immunological mechanisms (selective reactions [SRs]). SRs are thought to be induced by specific IgE antibodies or by T cells. In this manuscript, we focus on SRs, which are of great concern in children and adolescents and comprise a heterogeneous set of clinical pictures ranging from mild entities such as urticaria/angioedema to potentially life-threatening conditions such as Stevens-Johnson syndrome/toxic epidermal necrolysis.

Paracetamol and ibuprofen are the most frequent elicitors of IgE-mediated SRs, although pyrazolones have also been implicated. T cell–mediated reactions are infrequent in children but have been associated with ibuprofen, naproxen, and dipyrone.

In this review, we analyze the available literature on SRs in children and adolescents, with emphasis on epidemiological data, mechanisms, and drugs involved, as well as on diagnostic procedures.

Key words: Drug hypersensitivity reactions. NSAIDs. Single NSAID–induced urticaria/angioedema or anaphylaxis. Single NSAID–induced delayed reactions.

Resumen

A pesar de su eficacia en el tratamiento del dolor y la inflamación los antiinflamatorios no esteroideos (AINE), los medicamentos de mayor consumo mundial, también son la causa más frecuente de reacciones de hipersensibilidad a fármacos (RHFs) en cualquier tramo de edad. Aunque en muchas de estas reacciones se liberan mediadores inflamatorios en ausencia de reconocimiento inmunológico específico (intolerancia cruzada), un porcentaje considerable de las RHFs a AINE se producen a través de mecanismos inmunológicos (reacciones selectivas, SRs). En éstas participarían anticuerpos IgE específicos o células T. Las SRs son de gran interés en niños y adolescentes e incluyen un conjunto heterogéneo de entidades que comprenden desde manifestaciones clínicas de poca gravedad como la urticaria y el angioedema hasta otras como el síndrome de Stevens-Johnson y la necrolisis epidérmica tóxica, que pueden suponer una amenaza para la vida. En niños el paracetamol y el ibuprofeno son los medicamentos más frecuentemente implicados en las SRs mediadas por IgE aunque también se ha descrito la participación de las pirazolonas. Las reacciones mediadas por linfocitos T son menos frecuentes pero también se han descrito en relación con la administración de ibuprofeno, naproxeno y dipirona. En esta revisión analizaremos la literatura actual sobre las SRs en niños y adolescentes, centrándonos en los datos epidemiológicos, mecanismos y fármacos implicados, así como las pruebas disponibles para su diagnóstico.

Palabras clave: Reacciones de hipersensibilidad a fármacos. AINE. Reacciones selectivas. Urticaria/angioedema o anafilaxia inducidas por un único AINE. Reacciones tardías inducidas por un único AINE.

Introduction

Nonsteroidal anti-inflammatory drugs (NSAIDs) are widely used to control pain and fever and to treat various inflammatory diseases [1]. By inhibiting the synthesis of prostaglandins, they can induce both beneficial effects and adverse reactions [1], including type B reactions, which are not dose-dependent [2,3]. Type B reactions encompass drug hypersensitivity reactions (DHRs) to NSAIDs, which affect all age groups, including children and adolescents [4]. Paracetamol and ibuprofen are widely used in children [5-7], who can take all NSAIDs, including potent COX-1 inhibitors, as they grow older and enter adolescence.

The 2 most frequent types of hypersensitivity reactions to NSAIDs are cross-intolerance, which is related to an imbalance in the arachidonic acid pathway, and selective reactions (SRs), which are thought to be due to specific immunological mechanisms [8-11]. A recent new classification from the European Academy of Allergy and Clinical Immunology (EAACI) grouped all the clinical entities induced by hypersensitivity to NSAIDs reported to date [12]. In this manuscript, we focus on SRs, which can be differentiated into 2 groups:

1. Single NSAID–induced urticaria/angioedema or anaphylaxis (SNIUAA). This term applies when patients present urticaria and/or angioedema following the intake of a single NSAID or closely related drugs from the same group (eg, pyrazolones and diclofenac) but tolerate alternative, non–chemically related NSAIDs [8,9]. The reaction is independent of the strength of COX-1 inhibition, pointing to a specific immunological mechanism. These reactions usually occur within the first hour following drug intake, although this interval can be longer [13].
2. Single NSAID–induced delayed reactions (SNIDRs). SNIDRs comprise a highly heterogeneous group of clinical entities ranging from mild reactions, such as maculopapular exanthema (MPE), nonimmediate urticaria, and fixed drug eruption (FDE), to the potentially life-threatening Stevens-Johnson syndrome and toxic epidermal necrolysis (SJS/TEN). Reactions in this category differ from SNIUAA in terms of timing (>1 hour after intake) and clinical manifestations. The category also includes organ-specific reactions such as allergic hepatitis induced by drugs (eg, diclofenac) [14]. SNIDRs are sometimes mistaken for viral diseases [15].

The reactions included in both of these categories also appear in children and adolescents, although differences in severity, frequency, and drug involved have been detected in comparisons with adults [16,17].

In this review, we analyze current literature to discuss epidemiological data, as well as mechanisms and drugs involved, diagnostic procedures, and recommendations.

Epidemiology

Most articles dealing with adverse reactions to NSAIDs do not analyze in detail the underlying mechanisms or the various entities induced by these drugs. Up to 30% of DHRs caused by NSAIDs belong to the SNIUAA category [10], although figures vary depending on the study and the population evaluated [18,19]. No large population studies have been published for patients aged below 14 years, and the only available findings are from isolated case reports and small series [20]. Information is also scarce for SNIDRs, likely owing to their low prevalence. MPE is the most common manifestation in children and adolescents [21-23]. However, despite its temporal association with NSAIDs, it is often caused by other agents, such as viruses [15,24].

In our view, it is also relevant to include organ-specific reactions within SNIDRs, particularly those affecting the liver [25]. These reactions may be isolated or appear in the context of drug reactions with eosinophilia and systemic symptoms (DRESS) [26]; however, no appropriate epidemiological data are available on DRESS in children. This subgroup also includes drug-induced liver injury [27], pneumonitis [28], and aseptic meningitis [29], although to our knowledge, data on the prevalence of these entities in children are lacking.

Drugs Involved

The most commonly involved drugs in IgE-mediated reactions in adults are pyrazolones, followed by ibuprofen and diclofenac, although virtually all NSAIDs have been implicated. In general, many of the principles applicable for immediate hypersensitivity reactions to ß-lactams can be also applied in IgE-dependent reactions [30]. Paracetamol and ibuprofen are the most frequent elicitors of SNIUAA in children [31-34], although pyrazolones have also been implicated [20].

Despite the low frequency of SNIDRs in children, FDE has been reported with ibuprofen, naproxen, dipyrone, oxicams, nimesulide, and other NSAIDs [31,35-37]. A strong association has also been reported in children between FDE affecting the labial mucosa and therapy with naproxen and oxicams [35]. Bufexamac is a potential trigger of acute generalized exanthematous pustulosis (AGEP) [38]. Aspirin (ASA) has been shown to induce TEN [39], and other NSAIDs have been associated with an increased risk of SJS/TEN [40].

Photoallergic and phototoxic reactions can also be induced by NSAIDs [41], and, while infrequent, should be considered when treating children who have taken NSAIDs orally (eg, propionic acid derivatives and oxicams) or topically (eg, propionic acid derivatives, arylacetic acid derivatives, and other drugs such as bufexamac) [41-44].

The chemical structure of some COX-2 inhibitors is similar to that of sulfonamide derivatives, and it may be the case that children sensitized to these drugs will also respond to COX-2 inhibitors [37].

Also relevant is the observation that some cutaneous symptoms induced by DHRs, including those caused by NSAIDs, are not always clinically distinguishable from those elicited by viruses. This is particularly important in children, as the reaction may be due to an interaction between an NSAID and a viral infection [45-47]. Arylacetic acid derivatives (eg, diclofenac) [48], ibuprofen, and other propionic acid derivatives have been implicated in organ-specific reactions in children and adolescents [49].

Pathophysiology

In order to fully understand the specific immunologic mechanisms involved in SRs to NSAIDs (SNIUAA and SNIDRs), we must consider interactions between drugs and proteins. Drugs must bind to proteins to become immunogenic and induce an immune response [14]. The nature of this binding, whether covalent or not [50], is beyond the scope of this review.

NSAIDs bind to serum and cellular proteins [51,52], which often require previous generation of active metabolites [50]. For example, diclofenac, which is involved in DHRs in children, requires aromatic hydroxylation and acyl glucuronidation to bind proteins covalently [53]. The protein-drug adducts generated may be involved in anaphylactic, exanthematic, or severe skin reactions such as DRESS, as well as in organ-specific reactions such as hepatitis [50]. Although mainly reported in adults, these entities can occur in children and adolescents [26,27,38].

Propionic acid derivatives are probably the drugs most commonly involved in DHRs to NSAIDs and have been shown to produce protein adducts with cell and serum proteins. Although the structural details of these conjugates have not been sufficiently well described, it is thought that this process is required for the induction of an IgE-mediated or T-cell response [54].

SNIUAA

Evidence of specific IgE antibodies has been found for several NSAIDs. In one study, 27 of 28 ASA-sensitive patients had IgE to salicyloyl and O-methylsalicyloyl determinants [55]. Specific antibodies to ASA have also been reported [56-58].

Pyrazolones are used for analgesic purposes in adults and children in many countries, although they are not licensed in others. Where they are widely used, they are the most common culprit of SNIUAA, and the existence of specific IgE has been reported in some studies [59], but not in others [60]. Dipyrone, commonly known as metamizole, also induces reactions through the formation of specific IgE [61,62]. Propyphenazone has been demonstrated to induce specific IgE [63]. Interestingly, selectivity for this drug was independent of the recognition of dipyrone [63].

Diclofenac and other arylacetic acid derivatives can induce immediate selective reactions, particularly anaphylaxis [64-66]. However, a recent study was unable to find specific IgE to diclofenac conjugates in the sera of allergic individuals [67].

SNIDRs

NSAIDs involved in T cell–mediated reactions in children and adolescents include propionic acid derivatives, diclofenac, pyrazolones, ASA, and the recently introduced selective COX-2 inhibitors. Although less common in children, reactions have been reported, including FDE triggered by ibuprofen [31,68], paracetamol [68], and nimesulide [37]. DRESS induced by ASA [69] and AGEP induced by bufexamac [38] and paracetamol are associated with an increased risk of SJS/TEN [40]. Although SJS/TEN has frequently been reported to be induced by ibuprofen [70-72], it is difficult to identify NSAIDs as the culprit, since other drugs are often administered simultaneously [72].

In addition to these 5 major groups, other less common entities have been reported and may possibly be due to additional, as yet undefined mechanisms. For example, several NSAIDs, such as paracetamol, indomethacin, and some pyrazolone derivatives, have been implicated in serum sickness–like syndrome [73]. However, the definition of this entity is usually based on clinical symptoms rather than the underlying mechanisms, which remain unknown. For ß-lactams, recent evidence indicates that these responses are T cell–dependent [74]. Other reactions include organ-specific diseases (eg, hepatitis, pneumonitis, and aseptic meningitis) that can be attributed to T cells or other pathogenic mechanisms. Additional details can be seen elsewhere [25,75,76].

Characteristics of Clinical Entities

SNIUAA

Immediate selective responses that are presumably mediated by specific IgE [9] and sometimes confirmed as such [55,56] can appear at all ages [20]. In children, exposure to NSAIDs increases; this is a prerequisite for developing immediate responses [9]. As occurs with ß-lactams [77] and possibly with other drugs, anaphylaxis in children is milder, and severe reactions are less frequent, although they do occur [20].

The approach for evaluating children with suspected DHRs to NSAIDs often involves the administration of a drug other than the culprit drug. Therefore, many cases where a selective immediate reaction occurs are not diagnosed. It is also important to consider the natural evolution of the disease and the fact that IgE antibody levels decrease over time [62,78], thus leading to loss of sensitivity for a given patient despite a clear clinical history of reactions [62,78].

SNIDRs

The most common clinical SNIDR is MPE, followed by FDE and other reactions, which can be severe and even life-threatening [8]. Although the clinical manifestations of these entities have been described elsewhere [8], here we provide information that could be of particular relevance in children.

MPE consists of diffuse cutaneous erythema and areas of skin elevation, sometimes accompanied by angioedema, which can evolve to vesicles. Immunohistochemistry reveals the presence of a mononuclear cell infiltrate surrounding blood vessels, with a predominance of CD4 lymphocytes expressing several activation markers [79].

Skin biopsies from patients with nonimmediate NSAID-induced urticaria show a typical T-cell infiltrate supporting a T-cell effector phenomenon. Urticaria often presents as typical wheal and flare lesions with angioedema. This type of reaction, which is usually described for amoxicillin [74], has also been reported for NSAIDs [80].

NSAIDs are among the most common causes of FDE, which consists of erythematous patches that recur mainly at the same site on re-exposure to the offending drug [81].

Intradermal $CD8^+$ cells producing large amounts of IFN-γ seem to play a key role [82].

DRESS, which is also known as drug-induced hypersensitivity syndrome, is a serious reaction characterized by fever, cutaneous eruption, and the involvement of several internal organs that may lead to hepatitis, renal impairment, and hematologic abnormalities such as hypereosinophilia [83]. Triggering NSAIDs include ibuprofen and selective COX-2 inhibitors [84,85].

SJS/TEN is characterized by widespread destruction of the epithelium and mucous membranes [86] owing to massive apoptosis of keratinocytes with the formation of blisters containing natural killer and $CD8^+$ cells [87]. TNF-α, granzyme B, perforin, and Fas ligand have been found in the supernatant [88-91]. Activation of keratinocytes by IFN-γ makes T cells more sensitive to T cell–mediated cytolysis [92]. Further information can be found in a recent review [93]. Although uncommon, respiratory and gastrointestinal involvement has been reported in children with SJS/TEN [94].

Topical NSAIDs such as ketoprofen have been associated with contact dermatitis in adults [44]; however, this drug appears to be safe in children [95].

Evolution and Risk Factors

In the case of SNIUAA, it is reasonable to suspect that patients lose sensitivity over time [62,78,96], as occurs with ß-lactams and other drugs [96,97]. In vitro evidence indicates that patients with positive skin and basophil activation test results may have negative results in subsequent tests [62,96], although it is not clear whether this means they will be able to tolerate the drug. In the case of T-cell reactions, responses to drugs persist over long periods, and patients do not show a loss of sensitivity [98].

Although atopy was shown to be more frequent in both patients with aspirin-induced asthma and patients with selective reactions to pyrazolones [99], a recent study showed the atopic status of selective responders to be similar to that of a control group [10]. Increased use of drugs and a previous history of anaphylaxis are risk factors [100,101].

The predisposing factors for SNIDRs are not well known, although paracetamol may increase the risk of SJS/TEN [40]. Because T-cell reactions to drugs usually depend on the generation of active metabolites that can stimulate the immune system, certain metabolic patterns and specific HLA alleles may constitute risk factors. More details are given in a recent review [102].

Diagnostic Tests

The diagnostic tests used with SRs are based on immunological recognition of the drug in vivo or in vitro.

In Vivo Tests

Skin testing in SNIUAA consists of prick and intradermal tests using soluble drugs that can be applied on the back of younger children or on the forearm of adolescents [103,104]. Guidelines for skin testing have already been published [105] and are valid for all age groups, although compliance and the rate of false positives must be taken into account in children [105]. Because SRs are particularly uncommon in children, no studies reporting sensitivity and specificity are available for patients aged less than 14 years [3]. For adolescents, some recommendations can be extrapolated from studies in adults. In the case of pyrazolones, sensitivity to dipyrone has been shown to reach 85.7% [62], although in another study it was only 42.3% [106]. For propyphenazone, serum specific IgE was found in 58% of patients [63].

In the case of SNIUAA, in vitro tests for determination of IgE levels have not been successful, although some studies have been published for a limited number of drugs (eg, pyrazolones) [63]. Skin testing for delayed reactions to NSAIDs is also rather limited [107], with little known about its success rate in children and adolescents [108]. Finally, although in vitro tests for T cell–dependent responses do exist, they are rather complex to interpret; and further evaluation of their utility is required [109].

A number of publications provide precise guidelines for diagnosis of SNIDRs, including patch and intradermal testing [103,104]. Some of these tests can be used with children, although false-positive results may be more frequent [107]. Patch testing with ibuprofen, naproxen, ketoprofen, and piketoprofen at 2% and 5% (wt/wt) has been performed in a patient with FDE induced by ibuprofen. Readings were taken at 24, 48, and 72 hours, and the only positive result was for ibuprofen at 5% after 72 hours [31].

With respect to the diagnosis of photoallergy, we recommend a recently published consensus document [110].

In Vitro Tests

Given that SNIUAA is presumed to be IgE-mediated, immunoassays based on experimental or commercially available prototypes may be applicable. IgE to various NSAIDs has been reported in isolated cases and small series for ASA [56] and propyphenazone [63]. Experimental prototypes have also been developed for diclofenac, which is commonly used to treat SNIUAA [111]. However, convincing data have yet to be published [67].

Although ibuprofen frequently elicits immediate selective reactions in children and adolescents, no direct evidence of specific IgE has been obtained to date [9].

The basophil activation test has proven successful for anaphylactic reactions and urticaria induced by pyrazolones. Sensitivity is around 50% [111], although some studies have found higher values [106]. Studies carried out for patients with selective immediate reactions to these drugs have shown that if patients are followed over time, positive test results can become negative [62], as occurs with ß-lactams [111].

In the past, many studies were carried out to monitor acute phase responses in nonimmediate allergic reactions by taking peripheral blood and samples of the affected skin. In this type of reaction, several cell-populations home to the skin and generate the tissue infiltrate that is typical of such lesions [112]. This finding has been of value for differentiating between drug-induced and virus-induced diseases [45]. The procedures have not been sufficiently exploited to characterize the acute phase of DHRs in children. Monitoring of the acute phase can also be of value when attempting to distinguish between immediate

and nonimmediate reactions. Therefore, quantitation of tryptase in peripheral blood and N-methyl histamine in urine can prove useful when distinguishing between anaphylaxis and other types of nonallergic shock and for determining nonimmediate T cell–dependent responses [113].

Drug Provocation Test

In SNIUAA, drug provocation testing consists of the administration of incremental doses of the culprit drug at regular time intervals until an objective response that can be considered positive is obtained. In a recent study of children with a reaction suggestive of hypersensitivity to NSAIDs, oral challenge confirmed a selective mechanism in 14% of cases and cross-intolerance in 44% [114].

No consensus protocols exist for evaluating SNIUAA in children, although some studies propose algorithms that may be of value. Doña et al [10] gave patients alternative drugs. For example, in the case of anaphylaxis and/or urticaria induced by ibuprofen, the patients were given ASA; if this led to a reaction, they were classified as cross-intolerance [10]. If several episodes of anaphylaxis/urticaria occurred with the same drug (eg, ibuprofen or diclofenac) but the patient tolerated an alternative (eg, ASA), the case was classified as SNIUAA. However, if only 1 episode was reported and the alternative drug was well tolerated, controlled administration of the culprit drug was performed. Recent, related studies on children may be of interest to the reader, with additional information on dosages [20,114].

SNIDRs comprise the most heterogeneous group of entities induced by DHRs to NSAIDs. General rules are therefore not applicable, although it is now widely accepted that MPE, the most common clinical entity, may be challenged since it is a mild reaction [14,115]. Interestingly, many patients with MPE attributed to NSAIDs are later shown to have good tolerance, likely due to the wide range of other factors that can induce this entity [116]. The principle for challenge in this entity is to use increasing doses of the culprit drug until the recommended therapeutic dose is reached [117]. To reduce the risk of adverse effects, it is recommended to escalate the dose every 24-48 hours and check for symptoms indicative of a reaction [117]. In principle, challenge should be initiated in hospital, and patients should be monitored every time a dose is administered. This procedure can be carried out in an outpatient setting [117].

For FDE, providing that lesions are not too extensive, many centers also base diagnosis on challenge testing, particularly in cases where the patient is given several drugs. This procedure is more appropriate for identifying the culprit than for diagnosing the clinical entity [118,119].

Challenge testing is not recommended for the remaining clinical entities within this category, especially in the more severe reactions such as SJS/NET, AGEP, DRESS, and organ-specific reactions such as allergic hepatitis [120]. In these cases, the diagnosis should be based on the clinical history and histopathology data [14].

Differential Diagnosis

The differential diagnosis must include the time interval following contact with the trigger, which in many instances can be a drug other than NSAIDs or an allergen, usually an orally ingested food allergen, insect sting, or any other exposure that can trigger anaphylactic or urticarial reactions.

In SNIUAA, the time interval between drug intake and the occurrence of the episode is very short (usually less than 1 hour). Therefore, it is important to consider whether other drugs and/or food allergens have been taken at the same time as the NSAID [77,121].

Diagnosis of SNIDR can be complicated by viruses and bacteria capable of inducing clinical conditions that are indistinguishable from a drug reaction. Special attention must be paid to severe T cell–mediated reactions. For example, staphylococcal scalded skin syndrome can have a very similar clinical presentation to TEN and is more frequent in pediatric populations. However, the syndrome usually has less mucosal surface and internal organ involvement than TEN [122,123]. It is also important to note that although SJS and TEN belong to the same spectrum of severe delayed reactions, prognosis for patients with SJS is better, with fewer sequelae and lower mortality [124]. Generalized bullous FDE is another classic differential diagnosis of TEN, and differentiation relies mainly on the presence of primary lesions and the absence of constitutional symptoms in FDE [124]. Although erythema multiforme in children is mostly associated with infections by herpesvirus, it can also be induced by drugs, and both typical and atypical targets often appear in association with blisters, thus making it difficult to distinguish from SJS [125]. In children, SJS can also be induced by *Mycoplasma pneumoniae*, although it is not associated with erythema multiforme [126]. Monitoring the acute phase can be of value when attempting to elucidate the mechanisms underlying the reaction [116,127].

Treatment

Administration of an alternative drug is recommended in the case of SNIUAA [9]. For example, a child who experiences anaphylaxis after taking paracetamol should be able to tolerate COX-1 inhibitors [34]. However, drugs from the same chemical group as the culprit may also induce reactions owing to cross-reactivity, as occurs with arylpropionic agents (eg, ibuprofen and ketoprofen), arylacetic derivatives (eg, diclofenac and aceclofenac), and pyrazolones (eg, propyphenazone and dipyrone). Cross-reactivity between selective COX-2 inhibitors may also occur [9].

The concept of cross-reactivity in T cell–dependent reactions is more complex than for immediate IgE-dependent reactions, because reactivity in the former is often related to the drug-metabolite rather than to the parent drug [14]. The culprit drug can be readily identified based on patch and/or intradermal test results, which, if positive, indicate that the drug should be avoided [117,128]. However, given that these tests have low sensitivity, controlled administration remains necessary. Exceptions include cases such as multiple drug hypersensitivity syndrome, where patients may respond to several non–chemically related drugs [129]. However, this condition has seldom been reported in children.

Of particular interest is the treatment of severe reactions. In general, the sooner treatment and supportive measures are initiated, the better the chance of survival, although there is still

no consensus on the best treatment to use. Most expertise is from studies carried out in adults. In the case of TEN, patients must be managed in burn and/or intensive care units [130]. General measures include maintenance of fluids and electrolyte balance, regulation of temperature and evaporation, and potential administration of corticosteroids [130-132].

In a large study involving pediatric patients with SJS/TEN, the average hospital stay was more than 20 days [72]. Intravenous and oral corticosteroids were used at an equivalent dose of 1-2mg/kg/d of prednisolone. Intravenous immunoglobulin 1.1 g/kg has been used in patients with extensive skin lesions (around 70% of body area) [133]. In a series of 10 consecutive patients with TEN, specific CD95 blockade with intravenous immunoglobulin reversed disease progression in all cases [90]. However, as with adults, the lack of comparative studies prevents us from recommending the appropriate dose or from confirming the validity of this therapy. Furthermore, use in children remains controversial [134]. For TEN, avoidance of corticosteroids combined with debridement of necrotic skin and blisters and coverage of the affected area with human skin allograft could prove to be a successful and safe treatment strategy [135].

Complications of severe reactions in children include sepsis, respiratory distress, infections, and ocular injuries [130,135].

A general approach to severe reactions where the immune system plays a predominant role involves combinations of immunosuppressors [136]. Administration of corticosteroids is controversial. Pulse therapy with dexamethasone and other corticosteroids has been administered in widespread lesions [137], although several complications have been reported [138].

Following the publication by Viardet et al [90], who suggested that intravenous immunoglobulin could be of value for the treatment of SJS/TEN, many studies have shown varied responses [138-146]. One study suggested a dose of 3-4 g/kg [140]. A detailed analysis of various corticosteroid-based approaches (with or without intravenous immunoglobulin) has been published [147]. Other therapies have also been proposed for children [148,149]. Less severe SNIDRs, such as AGEP, DRESS, and FDE, are usually self-limiting conditions that resolve once the offending drug has been withdrawn. In the acute phase, supportive measures can consist of wet-to-dry dressings with drying and application of disinfectant solutions to avoid infection [150]. Some individuals may require topical corticosteroids for symptom relief or systemic treatment in more severe cases [150]. Systemic treatment is especially effective for AGEP [151].

Desensitization

Desensitization is seldom used in SRs in children and adolescents and is preferred for adults with cardiovascular diseases, stroke, and other diseases [152]. When indicated, the general rules for adults can be applied in children after adjusting for dose [153-155], although desensitization to paracetamol or ibuprofen is rarely needed in children. The dosage should be escalated slowly to prevent anaphylactic reactions.

Further Research

Although SNIUAA is largely thought to be IgE-mediated, the precise underlying mechanism needs to be clarified and other possibilities explored. IgE has only been detected for ASA [56] and propyphenazone [63]. Neither skin testing nor in vitro tests have been developed as a diagnostic tool for other NSAIDs. The major difficulty in developing these tests is identification of the specific triggering metabolite and its conjugation to a solid support.

Similar difficulties are seen in T-cell reactions, where the sensitivity of skin testing (intradermal or patch testing, or photopatch for photoallergic reactions) is generally low.

In the near future, the results of genetic and transcriptomic studies and advanced phenotyping are expected to shed new light on our understanding of SRs [156].

Concluding Remarks

NSAIDs are responsible for many DHRs in children [20], including specific immune-mediated reactions, mainly SNIUAA and, albeit to a lesser extent, SNIDRs. Since children often react to a single NSAID whilst tolerating others, attempts should be made to establish the culprit. This is particularly important when the child has taken NSAIDs simultaneously with other drugs or has been exposed to allergens. Paracetamol and ibuprofen are the most common triggers of these reactions. SNIDRs are T cell–mediated and occur much less often in children than in adults. In many instances, these reactions mimic viral reactions: this is particularly problematic if children are taking paracetamol, ibuprofen, or other NSAIDs. In most such cases, the drug is not the true underlying cause of the reaction, and controlled administration is required to verify tolerance.

Funding

JA Cornejo-García received funding from the Miguel Servet Program (Ref CP14/00034), and JR Perkins received funding from the Sara Borrell Program (Ref CD14/00242), both from the Carlos III National Health Institute, Spanish Ministry of Economy and Competitiveness (grants cofunded by the European Social Fund). The present study was supported by grants from the Carlos III National Health Institute, Spanish Ministry of Economy and Competitiveness (grants cofunded by the European Regional Development Fund), RD12/0013/0001 (Red de Investigación de Reacciones Adversas a Alérgenos y Fármacos, RIRAAF Network), FIS PI12/02247, FIS PI13/02598, and the Andalusian Public Health Service (PI-0279-2012 and PI-0463-2013).

Conflicts of Interest

The authors declare that they have no conflicts of interest.

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