Hypersensitivity to Non-Steroidal Anti-Inflammatory Drugs on a Pediatric Portuguese cohort

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Abbreviations:

DPT – Drug Provocation Test

EAACI – European Academy of Allergy and Clinical Immunology

ENDA – European Network on Drug Allergy

NSAID – Non-Steroidal Anti-Inflammatory Drug

SCAR - Severe Cutaneous Adverse Reactions

Abstract

Background: Non-steroidal anti-inflammatory drugs (NSAID)/analgesics (paracetamol) are among the most common causes of drug hypersensitivity reactions in children, with a reported prevalence of around 0.3% in the pediatric population.

Paracetamol and ibuprofen are the most commonly reported culprits in the pediatric population.

Our objective was to describe the allergy workup to NSAID/paracetamol of a pediatric population monitored in an allergy outpatient clinic.

Methods: Retrospective observational study by consulting the medical records of patients evaluated in a pediatric outpatient clinic with history of NSAID/paracetamol, between January 2016 to August 2022.

Results: A total of 43 patients have been evaluated for NSAID/paracetamol suspected allergy: 53.5% females, mean age of 9.8±5.1 years, 47.7% atopic. The drugs reported as culprits were: ibuprofen(75.6%), paracetamol(17.8%), metamizole(4.4%) and naproxen(2.2%) and clinical manifestations were mainly urticaria/angioedema and maculopapular exanthema.

Skin tests were performed in 7 patients: paracetamol(n=5) and metamizole(n=2), which were all negative. Fourty-six drug provocation tests were performed: 28 with the culprit drug and 18 with an alternative one; only 2 were positive (ibuprofen - culprit NSAID group): one immediate periorbital angioedema and one delayed lip edema with oropharyngeal tightness.

Conclusion: The investigation of allergy to NSAID/paracetamol in children remains a challenge. In our population, ibuprofen was the most common NSAID reported. There were only 2 (4.3%) mild reactions on DPT. We could allow the use of the culprit NSAID/analgesic in 11 patients and an alternative one in 9 patients.

This study highlights the importance of DPT in children for a correct diagnosis of NSAID hypersensitivity and selection of an alternative drug.

Key words: diagnostic workup; drug hypersensitivity; non-steroidal anti-inflammatory drugs; pediatric; urticaria

Impact Statement: Non-steroidal anti-inflammatory drugs are the second cause of drug hypersensitivity suspicions in children. As most of those suspicions are not confirmed after a diagnostic workup it is very important to perform a correct investigation in order to avoid unnecessary restrictions.

Introduction

Nonsteroidal anti-inflammatory drugs (NSAID) and beta-lactam antibiotics are among the most common causes of drug hypersensitivity reactions. The reported prevalence of NSAID/paracetamol hypersensitivity is about 6% in the general population and 0.3% in the pediatric population. Paracetamol and ibuprofen are the most commonly reported culprit agents in the pediatric population, as they are the most prescribed drugs in this age group. (1–8)

Atopy and atopic diseases (eg: rhinitis, eczema and asthma) are reported to be the most important risk factors for drug hypersensitivity reactions, both in adults and children. (2,4,6,8)

In the pediatric population, NSAID/paracetamol are mainly prescribed as antipyretics or anti-inflammatory agents during viral infections. Often in children, viral diseases are accompanied by a maculopapular rash, which can mimic an allergic reaction. For this reason, it is very important to clarify the drug allergy label in children, in order to avoid unnecessary restrictions. (1–4,7–15)

In the pediatric population, the clinical presentations of NSAID/paracetamol hypersensitivity reactions are diverse and may range from maculopapular exanthema or nonimmediate urticaria, to life-threatening reactions, as anaphylaxis or severe cutaneous adverse reactions (SCAR). (2–4,8,9,16–18)

The diagnostic workup includes a detailed clinical history with identification of the culprit drug, reaction time, clinical manifestations, treatment needed, other drugs taken, presence of comorbidities. The gold standard for the diagnosis of NSAID/ hypersensitivity is the drug provocation test (DPT). When an immediate immune reaction is suspected, skin tests (prick and intradermal) may be indicated, only validated for metamizole and paracetamol, but can be painful and poorly tolerated by children. In mild, nonimmediate reactions, it has been proposed to perform the DPT without prior skin tests. (1,2,8,9,14,15,19,20)

With this study, we aimed to: i) describe the characteristics and clinical manifestations of NSAID/ paracetamol allergy in a tertiary pediatric allergology outpatient clinic; ii) identify the main NSAID/analgesic reported as culprits; iii) describe the diagnostic workup performed in order to confirm/exclude the NSAID/ paracetamol allergy label.

Material and methods

Population and study design

Retrospective observational study including all children and adolescents (0-18 years old) with a suggestive history of NSAID/paracetamol hypersensitivity reaction that completed an allergy workup in the Pediatric Outpatient Clinic.

Data refer to a period of 7 years, from January 2016 to August 2022, and were collected from the records in the patients' clinical files.

Clinical characterization and allergy investigation

In addition to the demographic characteristics, the clinical evaluation included a complete clinical history with identification of the culprit drug (according to parents' reports), a detailed characterization of the reactions according to time (immediate - less than 1 hour to 6 hours after the last intake; delayed - more than 6 hours after the last intake) (2,7), clinical manifestations (maculopapular exanthema, urticaria/angioedema, gastrointestinal symptoms, and severe reactions such as anaphylaxis and SCAR) and the presence of atopy, defined by the presence of other allergic diseases such as rhinitis, asthma and/or atopic dermatitis, confirmed with positive skin prick tests and/or specific IgE for aeroallergens. No isolated respiratory symptoms were identified. (3,5)

Skin Prick and Intradermal Tests

Skin prick and intradermal tests (if negative prick test) were performed when there was a suspicion of an immediate immune reaction to paracetamol or metamizole, with the formulations and concentrations according to the EAACI/ENDA group. (2,19) Sodium chloride 0.9% was used as a negative control for both prick and intradermal tests and histamine 10mg/mL as a positive control for prick tests. The results were recorded after 20 minutes and considered positive if the largest diameter of the papule was equal to or greater than 3 mm for SPT and at least 3 mm wider than the initial papule with surrounding erythema for IDT. (2,14,21,22)

Drug Provocation Tests

In order to confirm or exclude the diagnosis of NSAID/paracetamol hypersensitivity, an open DPT was performed. In patients with an initial severe reaction (like anaphylaxis or SCAR) or with a strong suggestive history, a DPT with an alternative NSAID was performed. The DPT were performed in our Pediatric Outpatient Clinic, by oral route with three doses (1/10, 1/3 and 2/3 of the therapeutic dose) every 30 minutes, with the total cumulative dose calculated as individual therapeutic dose (adjusted to weight and age), either for immediate or delayed reactions, according to EAACI/ENDA group recommendations. (2,4,5,8,19) After the last dose administration, children remained under surveillance for 2 hours and delayed reactions surveillance was also carried out. Those patients with delayed reactions extended the administration at home according to the time of the initial reaction.

The DPT was considered positive when objective signs occurred: exanthema, urticaria, angioedema, rhinitis, bronchospasm/wheezing, cough, vomiting/diarrhoea. (3,5) In this case, the DPT was stopped and the reaction was immediately treated accordingly. If subjective symptoms occurred, the supervising physician decided either to repeat the last step, divide the next step into two doses, or proceed as planned. If the patient could complete the DPT without further objective signs or symptoms, the DPT was considered negative. (2,7,15)

Statistical analysis

Statistical analysis was performed with GraphPad Prism software version 8.00 (Graphpad Software Inc., San Diego, USA).

Descriptive analysis included the frequency of positive results (in percentage) for qualitative variables compared with the Fisher's test. For quantitative variables, the average ± standard deviation with 95% confidence intervals was described. Normality was verified by the Shapiro-Wilk and Kolmogorov-Smirnov tests. For the comparison between two unpaired groups, Mann-Whitney tests were used, or unpaired, depending on the situation. Values of $p<.05$ were considered significant.

Ethical issues

The clinical part of the study as well as *in vivo* tests were carried out as part of the clinical routine evaluation.

All caregivers and patients (if aged 16 years or older) signed an informed consent form before carrying out the investigation (either skin tests and/or drug provocation tests), which describes the possible use of anonymized data for studies purposes.

The study followed the recommendations of the Ethics Committee and of the World Medical Association (Declaration of Helsinki revised in 2013).

Results

A total of 43 patients were included (53.5% females, mean age of 9.8 ± 5.1 years old; mean age at the reaction of 7.1 ± 5.1 years old) that were referred to our Outpatient Clinic for a suspected NSAID/paracetamol hypersensitivity during the defined period. There was an average delay of 3 ± 3.8 years between the reaction and the referral. The clinical and demographic characterization of the population is described in **Table 1**.

Atopy was present in about half of the patients (47.7%), not associated with the severity of the first reaction.

Twelve patients had a presumptive diagnosis of concomitant infection [viral tonsillitis (n=6), acute sinusitis (n=4), epididymitis (n=1) and fever of unknown origin (n=1)], of which 4 were concomitantly taking other drugs at the time of the initial reaction, namely antibiotics (amoxicillin, cefotaxime, fluconazole, gentamicin, clotrimazole) and analgesics (tramadol).

According to parents' reports, the drug suspected of causing the reactions were: ibuprofen (n = 32; 74.4%), paracetamol (n = 8; 18.6%), metamizole (n = 2; 4.7%) and naproxen (n = 1; 2.3%).

Seven patients had more than one episode of drug hypersensitivity, either with the same or different NSAID.

Regarding the clinical manifestations of the reactions, 28 (65.1%) were immediate reactions and 15 (34.9%) were delayed reactions (**Table 1**).

The clinical manifestations of the reactions are detailed in **Table 1**. Four of the five patients with anaphylaxis were adolescents (>12 years of age at reaction), being ibuprofen the most frequent NSAID identified as the culprit. Severe reactions (like anaphylaxis and Stevens-Johnson syndrome) were reported with only ibuprofen or paracetamol.

In 7 patients with suspected immediate reaction (anaphylaxis or urticaria), skin prick and intradermal tests were performed before DPT. Of these 7 patients, 5 were tested with paracetamol and 2 with metamizole, and skin tests were all negative. Six patients performed DPT after the skin tests, which were all negative. One patient did not undergo DPT by choice.

The other patients were directly submitted to DPT.

We performed 46 DPT in 43 patients, in patients with both immediate and delayed reactions, only excluding the ones with SCAR: 28 (60.9%) with the culprit NSAID/analgesic and 18 (39.1%) with an alternative one (**Table 2**).

In the culprit NSAID group, the following DPT were performed: ibuprofen (n= 18); paracetamol (n= 8), metamizole (n= 1) and naproxen (n= 1). Two (7.1%) DPT were positive (both with ibuprofen), with the same clinical manifestations as in the first reaction: 1 immediate periorbital angioedema and 1 delayed lip edema with oropharyngeal tightness. All reactions resolved with oral antihistamine and no severe reactions were recorded.

Confirmation of reactions with ibuprofen by DPT occurred in those patients who did not have a concomitant diagnosis of infection in the initial reaction.

In the alternative NSAID group, the following DPT were performed: nimesulide (n= 10); paracetamol (n= 5); etoricoxib (n= 2) and celecoxib (n= 1). No reactions were recorded on these DPT.

Discussion

NSAID/paracetamol are among the most common causes of drug hypersensitivity reactions in children. According to the literature, the reported prevalence of NSAID/paracetamol hypersensitivity is lower in children than in adults and varies depending if it has been proven by DPT or based on clinical history. (2, 3,7,8,16,17)

The percentage of atopy differs in different studies, in a range between 30 to 60% of patients (1,2,6,9,10,17,20), although one study refers up to 93% of patients (4); in our study, we had about half of the population (47.7%) with atopy, which is in accordance with the literature.

The literature describes maculopapular exanthema and nonimmediate urticaria as the most frequent manifestations of NSAID hypersensitivity in children. Although in our study the most common symptom was urticaria, there was a higher proportion of nonimmediate urticaria, which is in accordance

with what is described in the literature and may be explained by differences in drug habits between countries. (2,3,8,10)

Concomitant infections, fever syndromes or the use of other drugs may play a role in the pathophysiology of hypersensitivity drug reactions, besides infections can mimic a real drug reaction. (1,2,14,23,24) In our study, a suspected infection was present in approximately 28% of the population, so a high percentage of suspicious could have resulted from manifestations of an underlying disease. In our population, positive DPT (4.3%) only occurred in patients with suspected reaction to NSAIDs/paracetamol, without concomitant infection. the A study with a larger sample will be needed to validate these results.

In our population, the most frequent reactions were urticaria (with and without angioedema), and maculopapular exanthemas. Similar data is described in previous studies, demonstrating that cutaneous reactions, such as maculopapular rash and non-immediate urticaria are the most common manifestations of hypersensitivity to NSAID/paracetamol in children. NSAIDs/paracetamol are among the most frequent causes of drug induced anaphylaxis, which is consistent to what we found in our cohort where, although the most frequent manifestations are mucocutaneous, anaphylaxis is present in about 11% of the population. (2–4,6,8)

In our study, the drug most frequently involved in the hypersensitivity reactions were ibuprofen (75.6%) and paracetamol (17.8%). Comparing with the literature, the frequency and type of NSAID involved varies, but it is unanimous that ibuprofen together with paracetamol are the main elicitors (2,3,7,14–16), with paracetamol being the most common in children younger than 6 years old, as occurred in our study. (3,14)

We also identified as culprits metamizole in two patients (4.4%) and naproxen in one patient (2.2%), drugs more often prescribed in older children, together with aspirin, nimesulide and COX-2 inhibitors. (16)

It is important to state that the differences observed regarding the culprit NSAID between studies reflect variations in prescription patterns and demographic differences of the studied populations.

Skin tests in children are poorly validated (extrapolated from adults), logistically demanding and can be painful. The most standardized NSAID skin tests are for metamizole, although some medications can be tested with non-irritating concentrations, as in the case of paracetamol. (4,6) Nowadays, the standard

use of skin testing for the diagnosis of NSAID hypersensitivity is not recommend. (1) In the literature, skin testing has been used for the diagnosis of immediate reactions to metamizole and paracetamol in children. (1) In our study, we performed skin tests with metamizole and paracetamol in children with immediate reactions.

Some authors propose as possible approach to perform an initial DPT with aspirin and, if negative, perform another one with the culprit drug. If the DPT with aspirin is positive, patients are directly defined as cross-intolerant and an alternative NSAID should be find. (7,11,16,17) However, it is important to state that, according to the prescription profile of our country, it is not usual to prescribe aspirin to children under 18 years old. For this reason, we generally do not perform DPT with aspirin. Although most COX-II inhibitors are not indicated for fever or for children under 12 years of age, their safety has been proven in this age group, mainly with nimesulide, meloxicam and etoricoxib, which were the NSAIDs tested in our population. (4,8,11,17) We only performed DPT with the culprit drug when the reactions were non-severe and only got two (4.3%) positive DPT (ibuprofen), with the same clinical manifestations as in the first reaction: 1 immediate periorbital angioedema and 1 delayed lip edema with oropharyngeal tightness, demonstrating its safety and feasibility.

Conclusions

Drug hypersensitivity reactions in children are an important topic of debate. Antibiotics and NSAIDs are the most common suspected drugs. It is during childhood that most people take NSAIDs for the first time, with paracetamol and ibuprofen being the most used.

In our study, the most common NSAID reported as culprit was the Cox-1 inhibitor ibuprofen, which is similar to what is described in the literature. There were 2 (4.3%) reactions on DPT, being mostly urticaria/angioedema, also according to other studies. Therefore, we could allow the use of the culprit NSAID in 11 patients and an alternative one in 9 patients.

This study highlights the importance of DPT in children for a correct diagnosis of NSAID/paracetamol hypersensitivity and selection of an alternative drug.

There are still few studies on hypersensitivity to NSAIDs/paracetamol in children, so the allergy workup keeps representing a challenge, being crucial to decide the clinical approach for each patient and try to stablish the culprit drug or alternative ones, so they do not need to perform unnecessary evictions.

For this reason, we believe that the presented data increases our knowledge about NSAID/paracetamol hypersensitivity in pediatric populations and provides information about the clinical characteristic of such patients, being the biggest case series from a single center in our country.

Consent to participate statement: Informed consent was obtained from all participants' caregivers.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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Data Availability Statement: All data generated or analyzed during this study are included in this article. Further enquiries can be directed to the corresponding author.

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Table 1 Clinical and demographic characterization of the first reactions.

Total number of patients	**43**
Age, years old	9.8 ± 5.1 [3-18]
Gender, female / male	23 (53.5) / 20 (46.5)
Age in the reaction, years old	7.1 ± 5.1 [1-16]
Atopy	21 (47.7)
Underlying infection	12 (27.3)
Suspected drug	
Ibuprofen	32
Paracetamol	8
Metamizole	2
Naproxen	1
Immediate / delayed reactions	28 (65.1) / 15 (34.9)
Clinical manifestations	
Urticaria/Angioedema	27
Maculopapular exanthema	6
Anaphylaxis	5
Gastrointestinal symptoms	4
Stevens-Johnson syndrome	1

Data presented as n (%), mean±SD. SD, standard deviation.

Table 2 Characterization of drug provocation tests performed.

Drug provocation test (DPT)	Drug	Reaction
Culprit drug (n= 28; 60.9%)	• 18 ibuprofen • 8 paracetamol • 1 metamizole • 1 naproxen	Ibuprofen: • 1 immediate periorbital angioedema • 1 delayed lip edema with oropharyngeal tightness
Alternative drug (n= 18; 39.1%)	• 10 nimesulide • 5 paracetamol • 2 etoricoxib • 1 celecoxib	No reactions were recorded