Pediatric Allergy and Immunology

ORIGINAL ARTICLE DRUG ALLERGY

Drug provocation tests in the diagnosis of hypersensitivity reactions to non-steroidal anti-inflammatory drugs in children

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To cite this article: Zambonino MA, Torres MJ, Muñoz C, Requena G, Mayorga C, Posadas T, Urda A, Blanca M, Corzo JL. Drug provocation tests in the diagnosis of hypersensitivity reactions to non-steroidal anti-inflammatory drugs in children. *Pediatr Allergy Immunol* 2013: **24**: 151–159.

Keywords
hypersensitivity; non-steroidal anti-inflammatory drugs; children; cross-intolerance; selective; drug provocation tests

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Accepted for publication 11 December 2012

DOI:10.1111/pai.12039

Abstract

Introduction: Hypersensitivity reactions to non-steroidal anti-inflammatory drugs (NSAIDs) are the most frequently reported reaction to drugs. They can be induced by pharmacological mechanisms (cyclooxygenase inhibition), with patients classified as cross-intolerant (CI), or by specific immunological mechanisms, IgE or T cell, with patients classified as selective reactors (SR).
Objective: To analyse a large group of children with a history of NSAID hypersensitivity diagnosed by drug provocation test (DPT).
Methods: A group of 63 children with a history of NSAID hypersensitivity were evaluated by DPT. The children were classified as CI or SR depending on the acetyl salicylic acid (ASA) response in DPT. The atopic status was also assessed by prick tests and total IgE in serum.
Results: Using DPT, 68.2% were confirmed as having hypersensitivity, 58.1% classified as CI and 41.9% as SR. Of the 119 DPT performed, 73 were positive (53.4% to ibuprofen, 37% to ASA, 8.2% to metamizol and 14% to paracetamol); angio-oedema was present in 86.3% of cases. All CI cases tolerated the administration of paracetamol. A significant number of the CI children were atopic compared with the SR children and non-allergic controls.
Conclusion: In these children, CI hypersensitivity to NSAIDs was the most frequent type of hypersensitivity reaction. Ibuprofen was the drug most often involved, angio-oedema the most common entity, and frequently associated with atopy. DPT proved a safe approach for diagnosing these patients.

Hypersensitivity reactions to non-steroidal anti-inflammatory drugs (NSAIDs) are the most frequently reported reaction to drugs; NSAIDs are followed by beta-lactam antibiotics and to a lesser extent other drugs (1–4). According to the revised nomenclature for allergy, these reactions are classified as allergic or non-allergic (5). Allergic reactions are those mediated by specific immunological mechanisms, whether IgE- or T-cell dependent, and the clinical response is induced by a single drug class of NSAIDs with good tolerance to other NSAIDs not chemically related (6–8). These patients are considered as selective reactors (SR). The most common hypersensitivity reactions are non-allergic, where no specific immunological recognition occurs, with the mechanism proposed being inhibition of the cyclooxygenase (COX) enzyme and the release of histamine and sulphidopeptide leukotrienes (9–12). In this group, chemically non-related NSAIDs induce the reaction and patients are classified as cross-intolerant (CI).

Hypersensitivity reactions to NSAIDs, both allergic and non-allergic, have been poorly studied in children as compared to adults. Moreover, it is thought that these reactions are less frequent at younger ages, attributed to the lower consumption of NSAIDs in children (13). Ibuprofen, a propionic acid derivative, is the most often consumed NSAID, together with paracetamol, a drug that although not considered a NSAID is

Abbreviations
NSAIDs non-steroidal anti-inflammatory drugs; SR selective reactors; COX cyclooxygenase enzyme; CI cross-intolerant; ASA acetyl salicylic acid; DPT drug provocation test; PT skin prick test; ENDA European Network for Drug Allergy; TCD total cumulative dose.

an inhibitor of prostaglandin synthesis (14). Acetyl salicylic acid (ASA) is not now widely used in children. Both ibuprofen and paracetamol have been considered safe medications as a result of a prospective study performed in 27,000 children younger than 2 yr of age (15). The reported prevalence of hypersensitivity reactions to NSAIDs in the general population is 0.3% in adults, with similar figures in children (10). To our knowledge, no further prevalence studies have yet been carried out in children.

Several studies have found that facial angio-oedema is the main clinical entity reported by children with NSAID hypersensitivity, especially in CI cases (16–21), with this symptom increasing in frequency with age till 21 yr of age (17). The diagnosis of these children is based on a clear clinical history or on an oral drug provocation test (DPT). With this approach, the rate of positive DPT responses varies greatly, ranging from <1% to nearly 50% (18, 20). Based on the clinical history and DPT, most cases had CI reactions (1, 12–14, 17, 20), with the response to paracetamol in these patients estimated at between 4 and 25% (21–23). Regarding the risk factors that can influence the development of NSAID hypersensitivity, atopy and clinical atopic disease have often been associated in both adults and children (1, 20, 21, 24). The reason for this has not been studied in detail.

The aim of this study was to evaluate a group of children with a clear history of hypersensitivity reactions to NSAIDs with diagnosis established by DPT. An analysis of the clinical data, including a detailed description of the sensitization profile, and the atopic status was also carried out.

Methods

Patients

We evaluated children with symptoms suggestive of hypersensitivity reactions to one or more NSAIDs. These patients were studied in the allergy unit of the paediatric department of Carlos Haya Hospital (Malaga, Spain) from 2008 to 2012.

Inclusion criteria

Patients aged 1–14 yr with a diagnosis suggestive of NSAID reactions. The procedure for establishing the diagnosis is described below.

Exclusion criteria

Patients older than 14 yr; suspicion or evidence of hypersensitivity reactions such as fixed drug eruption, erythema multiforme, Stevens–Johnson/toxic epidermal necrolysis complex or acute exanthematic pustulosis; chronic urticaria or acute recurrent urticaria not attributed to NSAID intake; patients who had acute infections and/or underlying diseases that contraindicated DPT; and patients who tolerated NSAIDs.

The study was conducted according to the principles of the Declaration of Helsinki and approved by the Hospital Ethics Committee. All participants were informed orally about the study and signed the corresponding informed consent.

Atopy status assessment

The atopy status was assessed with three parameters: a clinical questionnaire, a skin prick test (PT) and measurement of total IgE in serum samples. The clinical questionnaire included questions on nasal and bronchial symptoms: sneezing, itching, watery nose, nasal blockage, difficulty breathing, cough and wheezing. It also included clinical entities induced by food such as urticaria, angio-oedema, oral allergy syndrome, eczema, anaphylaxis or shock.

The PT was performed with a battery of 11 common allergens, including pollens, house dust mites, moulds, animal danders, peanut, nut and peach (ALK, Madrid, Spain). Histamine hydrochloride 10 mg/ml and phenolated glycerol-saline were used as positive and negative controls, respectively. A positive PT response was defined as a wheal diameter of 3 mm or larger to at least 1 of these allergens. The patients were requested to stop taking any medications that contained antihistamine at least 8 days before skin testing.

Total serum IgE was determined by ImmunoCAP (Phadia, Uppsala, Sweden), according to the manufacturer's instructions. A consensus cut-off value equal to or >130 IU/ml was used to classify the subjects as atopic or non-atopic.

The atopic status was also analysed in a group of 20 children with confirmed good tolerance to NSAIDs.

Oral drug provocation test

Oral DPT was performed in a single-blind procedure following the European Network of Drug Allergy (ENDA) recommendations (25). On the first evaluation, increasing doses of the culprit NSAIDs were administered orally at intervals of 60 min up to a total of three administrations in 1 day, depending on the drug (see Table 1). If cutaneous and/or respiratory symptoms or alterations in vital signs (rhythm alterations, decrease in peak expiratory flow rate or hypotension) appeared, the procedure was stopped and the symptoms were evaluated and treated. If no symptoms appeared during the DPT, the therapeutic dose was achieved. If good tolerance occurred, a therapeutic course of 2 days was given 24 h afterwards.

In those cases with a positive DPT to the culprit NSAID, a second evaluation was performed 1 wk later. Increasing doses of ASA were administered orally at intervals of 60 min up to a total of five administrations divided over 2 days (see Table 1). The clinical evaluation was the same as that performed with the

Table 1 Doses of NSAIDs used in the drug provocation tests

Drug	Doses used in DPT	Total cumulative dose (TCD)
Paracetamol	One dose	15 mg/kg/dose
Dipyrone	¼, ¼ and ½ of the TCD	20 mg/kg/dose
Ibuprofen	¼, ¼ and ½ of the TCD	10 mg/kg/dose
ASA	1st day: ¼, ¼ and ¼ of the TCD 2nd day: ½ and ½ of the TCD	20 mg/kg/dose

culprit drug. In those cases with a positive DPT to the culprit NSAID and ASA, and therefore considered as CI, tolerance to paracetamol was also assessed.

No DPT was performed with the culprit drug in patients with severe reactions (anaphylaxis or anaphylactic shock). In all cases, the episode reported by the patient had to have occurred at least 1 month before performing the DPT. FEV1 values had to be at least 80% of predicted values. Hourly measurements of peak expiratory flow with a Mini-Wright peak flow metre (Clement Clarke International Ltd., London, UK) performed on the day before challenge showed a variability of <20% in peak expiratory flow values in all subjects. Antihistamine agents were stopped 1 wk before the challenge.

Patient classification

Patients who experienced a DPT with two different NSAIDs were classified as CI and those who had a positive DPT with the culprit drug and good tolerance to ASA were classified as SR.

Statistical analysis

Comparisons for quantitative variables without normal distributions were made by the Mann–Whitney *U*-tests and between qualitative variables by the chi-squared test. All reported p values represented two-tailed tests, with values < 0.05 considered statistically significant.

Results

A total of 63 patients with a history compatible with hypersensitivity reactions to NSAIDs were evaluated over a 4-yr period (February 2008–February 2012). Of this group, 43 (68.2%) were confirmed as having hypersensitivity as they had a positive DPT to the culprit NSAID, whereas 20 (31.7%) had good tolerance to the culprit NSAID. The clinical characteristics of both groups of patients, with or without hypersensitivity, are shown in Table 2. Significant differences existed between those finally confirmed as having or not having hypersensitivity concerning the NSAID involved, type of reaction, interval between drug intake and appearance of symptoms, and number of episodes.

Of the 43 patients with confirmed hypersensitivity, 25 (58.1%) had a positive DPT to the culprit NSAID and to ASA and were therefore classified as being CI, whereas 18 (41.9%) were positive to the culprit NSAID with good tolerance to ASA and were therefore classified as SR. Table 3 shows the clinical characteristics of the two groups of patients. No significant differences were found between CI and SR for any of the variables analysed.

Of the 119 DPT performed, 73 (61.3%) were positive; a detailed description of the results is shown in Table 4. In these 73 cases, 39 had positive DPT with ibuprofen, 26 with ASA, 7 with metamizol and 1 with paracetamol. All the CI cases tolerated the administration of paracetamol. The clinical symptoms and the time intervals between drug administration and development of symptoms were similar to those reported by the patients for the original reaction, except in nine cases with angio-oedema: five CI patients (cases 6, 21, 27, 31 and 34) who also developed respiratory symptoms, mainly rhinoconjunctivitis, during the DPT, and four, 3 SR and 1 CI (cases 14, 38, 42 and 43), who also developed urticaria or exanthema. The reactions were usually mild and controlled by antihistamines (dexclorpheniramine: 0.04 mg/kg/dose) and corticosteroids (prednisolone: 1 mg/kg/dose). However, nine patients (cases 1, 3, 6, 14, 21, 25, 27, 31, 34 and 40) developed more severe symptoms that needed adrenaline (0.01 mg/kg intramuscular with 0.3 mg as maximum dose) to control the symptoms.

Comparisons between the positive DPT induced by the three NSAIDs (ibuprofen, ASA and metamizol) showed no significant differences concerning the clinical symptoms, although ASA was the drug most often inducing respiratory symptoms (26.9%) (Fig. 1). Analysis of the total cumulative dose (TCD) before development of symptoms in the DPT, in terms of percentage, showed significant differences at the 75% TCD level ($p = 0.003$), where 53.8% of the responders were positive

Table 2 Clinical and demographic characteristics of the patients evaluated

	Hypersensitivity	No hypersensitivity	p
(N, %)	43 (68.2)	20 (31.7)	
Age (years, median, IR)	9 (6.1–11.3)	9 (5.8–11.5)	0.267
Sex (male, N)	30 (69.7)	13 (65)	0.707
Fever (yes, N, %)	20 (46.5)	14 (70)	0.084
Interval reaction-study (days, median, IR)	63 (34.7–92.5)	64.5 (27.3–115.1)	0.490
Drug involved (N, %)			
Ibuprofen	41 (82)	15 (68.2)	0.045
Paracetamol	1 (2)	4 (18.2)	
ASA	1 (2)	1 (4.5)	
Pyrazolone	7 (14)	2 (9.1)	
Type of reaction (N, %)			
Angio-oedema	40 (80)	6 (27.3)	0.000
Angio-oedema + asthma	2 (4)	0 (0)	
Angio-oedema + Urticaria	2 (4)	2 (9.1)	
Urticaria	2 (4)	3 (13.6)	
Exanthema	4 (8)	9 (40.9)	
Asthma	0 (0)	2 (9.1)	
Interval to the reaction			
Immediate (<1 h)	43 (86)	7 (31.8)	0.000
Non-immediate (>1 h)	7 (14)	15 (68.2)	
Number of episodes (median)	1.91	1.25	0.031

Table 3 Clinical and demographic characteristics of the patients with NSAID hypersensitivity classified as cross-intolerant (CI) cases or selective reactors (SR)

	CI	SR	p
(N, %)	25 (58.1)	18 (41.9)	
Age (years, median, IR)	9 (6.8–11.3)	8 (6.1–11.9)	0.569
Sex (male, N)	18 (72)	12 (66.6)	0.747
Fever (yes, N, %)	11 (44)	9 (50)	0.763
Interval reaction-study (days, median, IR)	63 (35.7–90.1)	64 (33.4–92.4)	0.681
Drug involved (N, %)			
Ibuprofen	25 (84)	16 (80)	0.171
Paracetamol	0 (0)	1 (5)	
ASA	0 (0)	1 (5)	
Pyrazolone	5 (16)	2 (10)	
Type of reaction (N, %)			
Angio-oedema	26 (86.7)	14 (70)	0.102
Angio-oedema + asthma	2 (6.7)	0 (0)	
Angio-oedema + Urticaria	0 (0)	2 (10)	
Urticaria	0 (0)	2 (10)	
Exanthema	2 (6.7)	2 (10)	
Asthma	0 (0)	0 (0)	
Interval to the reaction (N, %)			
Immediate (<1 h)	26 (86.7)	17 (85)	0.683
Non-immediate (>1 h)	4 (13.3)	3 (15)	
Number of episodes (median)	2.12	1.61	0.191

to ASA, 14.3% to metamizol and 2.6% to ibuprofen (Fig. 2). Considering the time interval between drug intake and appearance of symptoms, significant differences ($p = 0.019$) were found between drugs; the shortest time was with ASA (median: 35 min; IR: 20–60), followed by ibuprofen (median: 60 min; IR: 25–75) and metamizol (median: 120 min; IR: 60–125) (Fig. 3).

The atopic status was analysed considering one criterion (PT to inhalant allergens) and the combination of two (PT to inhalant allergens plus clinical symptoms) and three criteria (PT to inhalant allergens plus clinical symptoms and total IgE >130 IU/ml) in CI cases, SR and controls (Table 5). Significant differences were found between CI cases and SR and controls when PT to at least one allergen was considered. These differences were also observed after a positive PT to at least one allergen and prick + clinical symptoms + IgE >130 IU/ml were considered and almost significant when only PT + clinical symptoms was considered. Regarding the clinical entities noted, although there was a higher proportion of rhinitis, asthma and food allergy, the differences were only significant for food allergy. A more detailed analysis of the skin test results to prevalent inhalants and food allergens (Table 6) showed that the inhalants most often detected as positive were *D. pteronyssinus, D. farinae*, olea pollen and alternaria ($p < 0.05$).

Discussion

In this study, we evaluated a group of children with a history compatible with hypersensitivity reactions to NSAIDs and the diagnosis confirmed by DPT. We found that nearly 70% of the cases had hypersensitivity. This is an important percentage when compared with previous reports in children (16, 18, 20). These differences can be attributed to the consistency of the symptoms reported, the number of cases studied and the lack of performance of DPT in all cases. Of the cases finally confirmed as hypersensitive and based on the DPT results with ASA, 58% were classified as being CI and 41.9% as SR. The percentage of CI cases was lower than that detected among adults in the same Spanish population (2) or French children, where 76% and 69% CI cases were found, respectively (20). Because in our study in addition to a compatible clinical history, all cases were confirmed by a DPT, more accurate data were obtained, suggesting overestimation of CI cases in those studies where no DPT was carried out. In fact, a recent study showed that with a clinical history based on one or two episodes, even if the history is very clear, there may still be good tolerance to a DPT (26).

As in previous studies (16–21), angio-oedema (80%) was the most reported symptom in children with confirmed NSAID hypersensitivity, differing significantly with those finally confirmed as tolerant (20%), who also reported symptoms indicative of urticaria or exanthema. In those cases finally classified as not having hypersensitivity, 70% of the symptoms appeared in the context of fever, showing a possible interaction between the drug and the infectious agents responsible for the symptoms. This phenomenon may be similar to that described in children who experience exanthema or urticaria during beta-lactam intake, even though most of them are eventually confirmed as non-allergic by DPT with beta-lactams (27). Of note was the fact that, in contrast to what occurs in adults, angio-oedema was the most common entity reported (2). Whether this represents another entity and/or a different mechanism is not known at present. The explanation given for urticaria/angio-oedema is also related to COX inhibition in the sulphidopeptide leukotriene pathway, although no studies have yet been carried out exclusively in angio-oedema.

Ibuprofen was the most common NSAID involved in the reactions finally confirmed by DPT. This is in agreement with previous results indicating that ASA is not nowadays the most common inducer (19–21). In our population, pyrazolones were also involved because they are still consumed. Regarding paracetamol, we only found one case that developed a selective reaction to this drug.

The response to paracetamol in CI subjects has been reported to be up to 25% in children (20–23) and 34% in adults (28). However, in our series, we did not find any cross-intolerance to this drug. Reasons for this difference include the way patients are classified, as in many studies the result is based solely on the clinical history or that paracetamol sensitivity may appear in the evolutive course of the disease. Nevertheless,

Table 4 Clinical characteristics and drug provocation test results in patients with hypersensitivity reactions

Pat	Age (years)	Type	Reaction	NSAID	DPT	Reaction DPT	Dose (% TCD)	Interval (min)
1	12	SR	ANG	Ibuprofen	Ibuprofen (+) ASA (−)	ANG	100%	720
2	11	CI	ANG	Ibuprofen	Ibuprofen (+) ASA (+) Paracetamol (−)	ANG ANG	50% 50%	20 20
3	7	CI	ANG	Ibuprofen	Ibuprofen (+) ASA (+) Paracetamol (−)	ANG ANG	100% 100%	60 60
4	8	CI	ANG	Ibuprofen	Ibuprofen (+) ASA (+) Paracetamol (−)	ANG ANG	100% 50%	20 60
5	14	SR	ANG	Ibuprofen	Ibuprofen (+) ASA (−)	ANG	100%	30
6	10	CI	ANG	Ibuprofen	Ibuprofen (+) ASA (+) Paracetamol (−)	ANG + RC ANG + RC	100% 100%	1440 720
7	11	CI	ANG	Ibuprofen	Ibuprofen (+) ASA (+) Paracetamol (−)	ANG ANG	100% 100%	180 180
8	10	CI	ANG ANG	Ibuprofen Metamizol	Ibuprofen (+) Metamizol (+) ASA (+) Paracetamol (−)	ANG ANG ANG	100% 100% 75%	60 125 25
9	10	SR	ANG	ASA	ASA (+) Ibuprofen (−)	ANG	75%	20
10	6	SR	ANG ANG	Ibuprofen Metamizol	Metamizol (+) Ibuprofen (−) ASA (−)	ANG	100%	60
11	6	SR	ANG	Ibuprofen	Ibuprofen (+) ASA (−)	ANG	100%	60
12	9	CI	ANG	Ibuprofen	Ibuprofen (+) ASA (+) Paracetamol (−)	ANG ANG	100% 75%	60 15
13	11	SR	ANG	Ibuprofen	Ibuprofen (+) ASA (−)	ANG	100%	25
14	8	SR	ANG	Ibuprofen	Ibuprofen (+) ASA (−)	ANG + EXAN	100%	15
15	5	SR	URT	Ibuprofen	Ibuprofen (+) ASA (−)	URT	100%	45
16	9	CI	ANG ANG	Ibuprofen Metamizol	Ibuprofen (+) Metamizol (+) ASA (+) Paracetamol (−)	ANG ANG ANG	100% 75% 100%	240 35 20
17	10	CI	EXAN	Ibuprofen	Ibuprofen (+) ASA (+) Paracetamol (−)	EXAN EXAN	100% 75%	120 25
18	8	SR	ANG	Ibuprofen	Ibuprofen (+) ASA (−)	ANG	100%	45
19	12	CI	ANG	Ibuprofen	Ibuprofen (+) ASA (+) Paracetamol (−)	ANG ANG	100% 75%	15 10
20	7	CI	ANG	Ibuprofen	Ibuprofen (+) ASA (+) Paracetamol (−)	ANG ANG	100% 75%	75 10

Table 4 (Continued)

Pat	Age (years)	Type	Reaction	NSAID	DPT	Reaction DPT	Dose (% TCD)	Interval (min)
21	8	CI	ANG	Ibuprofen	Ibuprofen (+)	ANG	100%	360
					ASA (+)	ANG + RC	100%	60
					Paracetamol (−)			
22	14	CI	ANG	Ibuprofen	Ibuprofen (+)	ANG	100%	180
					ASA (+)	ANG	75%	45
					Paracetamol (−)			
23	11	SR	ANG	Ibuprofen	Ibuprofen (+)	ANG	50%	20
					ASA (−)			
24	10	CI	ANG	Ibuprofen	Ibuprofen (+)	ANG	100%	75
			ANG	Metamizol	Metamizol (+)	ANG	100%	90
					ASA (+)	ANG	75%	50
					Paracetamol (−)			
25	9	CI	ANG + ASTH	Ibuprofen	Ibuprofen (+)	ANG	100%	120
			ANG	Metamizol	ASA (+)	ANG + ASTH	75%	20
					Metamizol (+)	ANG	100%	120
					Paracetamol (−)			
26	9	CI	ANG	Ibuprofen	Ibuprofen (+)	ANG	100%	75
					ASA (+)	ANG	100%	60
					Paracetamol (−)			
27	9	CI	ANG	Ibuprofen	Ibuprofen (+)	ANG + RC	100%	60
					ASA (+)	ANG + RC	100%	20
					Paracetamol (−)			
28	8	SR	ANG	Ibuprofen	Ibuprofen (+)	ANG	50%	30
					ASA (−)			
29	7	SR	URT	Ibuprofen	Ibuprofen (+)	URT	50%	25
					ASA (−)			
30	6	SR	ANG	Ibuprofen	Ibuprofen (+)	ANG	25%	20
					ASA (−)			
					Paracetamol (−)			
31	8	CI	ANG	Ibuprofen	Ibuprofen (+)	ANG + URT + RC	50%	40
					ASA (+)	ANG + RC	50%	80
					Paracetamol (−)			
32	12	SR	ANG + URT	Ibuprofen	Ibuprofen (+)	URT	25%	10
					ASA (−)			
33	8	CI	ANG	Ibuprofen	Ibuprofen (+)	ANG	75%	50
					ASA (+)	ANG	100%	60
					Paracetamol (−)			
34	9	CI	ANG	Ibuprofen	Ibuprofen (+)	ANG + RC	100%	30
					ASA (+)	ANG + ASTH + RC	75%	40
					Paracetamol (−)			
35	8	SR	ANG + URT	Ibuprofen	Ibuprofen (+)	ANG	50%	40
					ASA (−)			
36	10	CI	ANG	Ibuprofen	Ibuprofen (+)	ANG	100%	240
					ASA (+)	ANG	75%	15
					Paracetamol (−)			
37	12	SR	EXAN	Ibuprofen	Metamizol (+)	EXAN	100%	360
			EXAN	Metamizol	Ibuprofen (−)			
38	6	CI	ANG	Ibuprofen	Ibuprofen (+)	ANG + URT	100%	60
					ASA (+)	ANG + URT	50%	120
					Paracetamol (−)			
39	11	CI	EXAN	Ibuprofen	Ibuprofen (+)	EXAN	100%	15
					ASA (+)	ANG	75%	30
					Paracetamol (−)			
40	6	CI	ANG + ASTH	Ibuprofen	Ibuprofen (+)	ANG + RC	100%	60
			ANG	Metamizol	Metamizol (+)	ANG	100%	120
					ASA (+)	ANG + ASTH	75%	50
					Paracetamol (−)			

Table 4 (Continued)

Pat	Age (years)	Type	Reaction	NSAID	DPT	Reaction DPT	Dose (% TCD)	Interval (min)
41	8	CI	ANG	Ibuprofen	Ibuprofen (+) ASA (+) Paracetamol (−)	ANG ANG	100% 75%	60 20
42	7	SR	ANG	Paracetamol	Paracetamol (+) ASA (−)	URT	100%	1440
43	8	SR	ANG	Ibuprofen	Ibuprofen (+) ASA (−) Paracetamol (−)	URT	50%	40

SR, selective reactors, CI, cross-intolerant; ANG, angio-oedema, URT, urticaria; EXAN, exanthema; ASTH, asthma; RC, rhinoconjunctivitis; DPT, drug provocation test; TCD, total cumulative dose.

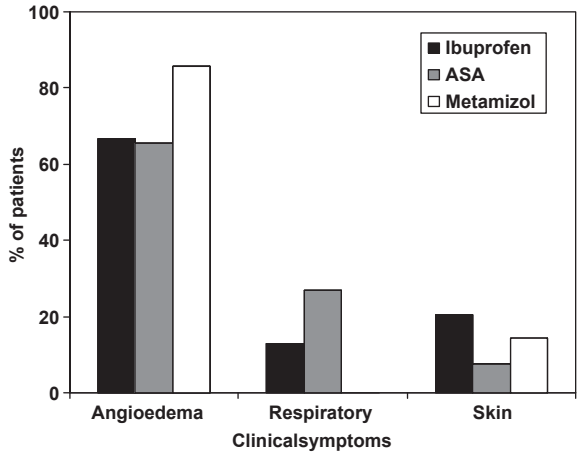

Figure 1 Percentage of patients who developed during the drug provocation tests clinical symptoms of angio-oedema, respiratory symptoms (asthma or rhinoconjunctivitis with or without angio-oedema) and cutaneous symptoms (urticaria or exanthema accompanying or not angio-oedema) with ibuprofen, ASA or metamizol.

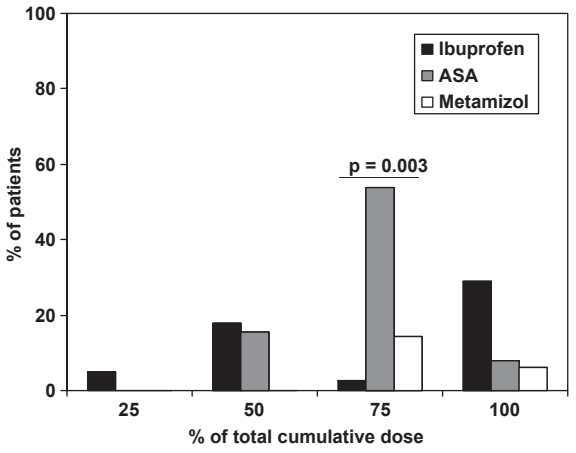

Figure 2 Percentage of patients responding to different percentages of the total cumulative dose (25, 50, 75 and 100) during the drug provocation tests with ibuprofen, ASA or metamizol.

these results indicate that paracetamol is safe in this population, although a DPT is recommended to verify this. It is important to check for paracetamol tolerance in all children with cross-intolerance to NSAIDs because there is no other approved medication for the treatment of fever or inflammation.

Analysis of the DPT results showed that the clinical symptoms and the time interval between drug administration and development of the symptoms were similar after the DPT to those reported for the original reaction. The most usual reaction was angio-oedema, except in some CI patients where the DPT was followed by respiratory symptoms, mainly rhinoconjunctivitis, and in some SR who experienced cutaneous symptoms. The fact that ibuprofen was the most common culprit drug and that the positive DPT response was induced by ASA, a stronger COX inhibitor (3), may explain the more intense response. This is confirmed because the response to

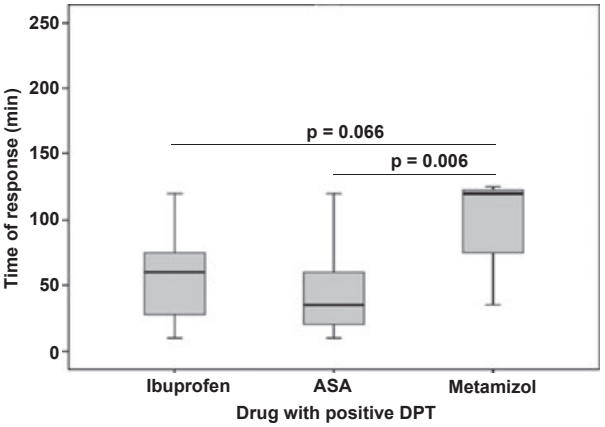

Figure 3 Box plot analysis representing the time to response in minutes after the drug provocation tests with ibuprofen, ASA or metamizol.

Table 5 Analysis of the atopic status in patients with hypersensitivity reactions (CI and SR) and a group of controls

Atopy criteria and entities	CI N (%)	SR N (%)	Controls N (%)	p
Prick positive to at least one allergen	18 (72)	5 (27.7)	6 (30)	0.004
Prick + clinical symptoms	14 (56)	4 (22.2)	6 (30)	0.064
Prick + clinical symptoms + IgE >130 IU/ml	12 (48)	1 (5.5)	4 (20)	0.005
Rhinitis	7 (28)	1 (5.5)	4 (20)	0.213
Asthma	5 (20)	1 (5.5)	2 (10)	0.410
Food allergy	5 (20)	0 (0)	0 (0)	0.037
Atopic dermatitis	5 (20)	4 (22.2)	2 (10)	0.647

Table 6 Skin prick test results to the different allergens tested in patients with hypersensitivity reactions (CI and SR) and a group of controls

Positive skin tests	CI N (%)	SR N (%)	Controls N (%)	p
D. farinae	9 (36)	3 (16)	1 (5)	0.035
D. pteronyssinuss	12 (48)	3 (16)	2 (10)	0.011
Phleum	7 (28)	3 (16)	4 (20)	0.742
Olea europea	15 (60)	2 (11.1)	5 (25)	0.002
Parietaria	7 (28)	2 (11.1)	3 (15)	0.372
Cat dander	6 (24)	2 (11.1)	2 (10)	0.462
Alternaria	13 (52)	1 (5.5)	4 (20)	0.003
Nut	6 (24)	0 (0)	2 (10)	0.053
Peanut	5 (20)	0 (0)	2 (10)	0.115
Peach	1 (4)	0 (0)	1 (5)	0.981

ASA appears faster and at a lower TCD. These results are in agreement with others (20) showing that after DPT, children responded to lower concentrations of ASA, followed by ibuprofen and paracetamol. However, these authors found no equivalent results for the time interval, which was shorter with paracetamol, followed by ibuprofen and ASA, differences probably due to the fact that they analysed CI cases and SR together.

Finally, regarding the atopic status, we found that CI patients had a higher percentage of positive PT to inhalant allergens, clinical symptoms of rhinitis and asthma, and total IgE when compared with the SR allergic to NSAIDs and non-allergic controls. PT results were higher to house dust mite, olea pollen and alternaria. These data are in agreement with previous results showing that atopy is associated with CI hypersensitivity reactions to NSAIDs in children and adults, affecting up to 90% of cases in some studies (2, 20, 21, 23, 24, 29–32). Most studies have detected a strong association with house dust mites, probably reflecting this more common sensitizer (2, 20, 21, 23, 24, 29–32). The reason for this association between atopy and persons CI to NSAIDs is not known, although it has been suggested that genetic factors may be involved. In fact, genes implicated in the IgE response (IL-4, IL-5 and IL-13) are located in the same chromosomal region as the cysteinyl leukotriene (LTC4S) (33, 34). We also detected an increase in food allergy in the group of CI patients, with a higher percentage of positive PT to nuts. Although less usual, NSAIDs have, nevertheless, been shown to increase food hypersensitivity, whether or not facilitated by exercise (35, 36).

In conclusion, we evaluated a large number of children with hypersensitivity reactions to NSAIDs confirming the diagnoses of cross-intolerance or selective reactors in all cases by drug provocation tests. Our results confirm that ibuprofen is the drug most often involved in the reaction, that angio-oedema is the typical symptom and that atopy, and not just to house dust mite, is often associated with cross-intolerant reactions.

Acknowledgments

We thank Ian Johnstone for help with the English language version of the manuscript.

Funding sources

This study was supported by grants from the Spanish Health Ministry Fund for Health in Spain (FIS) network RIRAAF (RD07/0064), PS09/02419, Junta de Andalucia (CTS 06603) and FIS (09/01768).

Conflict of interest

None of the authors has any conflict of interest. None received money for the present study. Research is part of their daily activities. All authors had full access to all the data (including statistical reports) and can take responsibility for the integrity of the data and the accuracy of the data analysis.

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