

Characteristics of subjects experiencing hypersensitivity to non-steroidal anti-inflammatory drugs: patterns of response

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Clinical & Experimental Allergy

Summary

Background Non-steroidal anti-inflammatory drugs (NSAIDs) are one of the most frequently involved groups of medicines in hypersensitivity drug reactions. Two mechanisms can induce the reaction: immunological (sensitization) due to a specific IgE or T cell response and pharmacological (cyclooxygenase inhibition). The contribution of each of these mechanisms to the reactions is not well known.

Objective To analyse a large group of subjects with confirmed hypersensitivity reactions to NSAIDs.

Methods The drugs involved, the clinical entities induced and the time interval between drug intake and appearance of the reaction were studied. In cases where the diagnosis was not confirmed, a drug provocation test was carried out. Atopy status was also assessed with prick test and total IgE in serum.

Results A total of 659 patients were finally considered to have had hypersensitivity reactions to NSAIDs; 76% had cross-intolerance (CI) and 24% were selective responders (SR). The most important drugs involved in CI were propionic acid derivatives, in most cases ibuprofen, and in SR pyrazolones. In CI, the most frequent clinical entity was urticaria and angio-oedema and to a lesser extent airway involvement. The skin and airways were both involved in an important proportion of cases. The most frequent entities in SR were urticaria and/or angio-oedema followed by anaphylaxis. Atopy was significantly associated in the CI group ($P < 0.005$).

Conclusion and Clinical Relevance Cutaneous hypersensitivity reactions by CI to NSAIDs are the most frequent entities induced by these compounds. In addition to aspirin, other NSAIDs are taking on a predominant role. Atopy can be a predisposing factor in patients with CI.

Keywords cross-intolerance, drug provocation test, nasal aspirin provocation test, non-steroidal anti-inflammatory drugs, selective hypersensitivity

Submitted 5 July 2010; **revised** 3 September 2010; **accepted** 6 October 2010

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Cite this as: I. Doña, N. Blanca-López, J. A. Cornejo-García, M. J. Torres, J. J. Laguna, J. Fernández, A. Rosado, C. Rondón, P. Campo, J. A. Agúndez, M. Blanca and G. Canto, *Clinical & Experimental Allergy*, 2011 (41) 86–95.

Introduction

Non-steroidal anti-inflammatory drugs (NSAIDs) are one of the most frequently involved groups of medicines in hypersensitivity reactions to drugs [1, 2]. These types of reactions include several clinical entities with different mechanisms leading to the release of inflammatory mediators. Reactions where symptoms occur within a short time after drug exposure are usually induced by the release of histamine and other vasoactive mediators [3].

Two groups have been described: the most common, where chemically distinct (non-related) drugs induce the reaction, with patients usually being classified as having cross-intolerance (CI) [2]; and the other group, where the response is induced by a single drug and the patients have good tolerance to other chemically unrelated compounds; these patients are classified as selective responders (SR) [4–6].

Most studies on CI to NSAIDs have focused on respiratory responses [7, 8], with the inhibition of the

cyclooxygenase (COX) enzyme and the release of histamine and sulphidopeptide leukotrienes being the proposed mechanism for these reactions [7]. This mechanism has also been proposed for cases of urticaria and angio-oedema induced by several NSAIDs [9]. Another clinical entity is the reactivation of pre-existing urticaria. In fact, chronic urticaria can be worsened by NSAIDs [2]. This may explain the appearance of symptoms from hours to several days after taking the drug. Although respiratory symptoms can be accompanied by cutaneous manifestations, especially in the more severe cases, cutaneous manifestations alone in the absence of respiratory involvement induced by different NSAIDs also exist. Surveys and clinical evidence indicate that urticaria is a common problem [10]; NSAIDs not only re-aggravate pre-existing urticaria but they can also induce urticaria and/or angio-oedema as the sole manifestation in subjects with no history of pre-existing urticaria in a significant number of cases [10].

In addition to CI mechanisms, selective reactions to these drugs also occur [5]. One of the major difficulties in studying allergic IgE reactions to NSAIDs is the lack of an *in vitro* test to determine the presence of specific antibodies and the low sensitivity of *in vivo* tests. For specific IgE to aspirin-induced asthma (AIA), an experimental prototype for detecting IgE has been developed [6], as well as for propyphenazone [4] and diclofenac [11]. Specific reactions also occur to selective COX-2 inhibitors [12]. Studies using basophil activation tests support an IgE mechanism in the case of dypirone [13]. In addition, for those cases with reactions occurring 24–48 h or longer after drug intake that usually respond to a single drug with good response to other NSAIDs, a T cell-mediated mechanism has been proposed [14].

Considering the above, we analysed a large number of patients referred to the allergy department of the participating hospitals with different types of hypersensitivity reactions to NSAIDs. The referral centre submitted patients with all types of adverse reactions compatible with hypersensitivity that included cutaneous and/or respiratory involvement. After careful evaluation, different procedures were carried out to establish the diagnosis. Results indicated that the most frequent entity was urticaria and/or angio-oedema due to CI followed by the same entities in SR, and to a lesser extent airway responders. Other drugs, such as ibuprofen, have now surpassed ASA in eliciting reactions.

Methods

Patients

We performed a multicentre allergological study within the RIRAAF Network (research network of allergic reactions to allergens and drugs), evaluating patients with

symptoms suggestive of hypersensitivity reactions to one or more NSAIDs. These patients were assessed in the allergy departments of five clinical centres in Spain (Carlos Haya Hospital, Malaga; Infanta Leonor Hospital, Madrid; Elche Hospital, Elche, Alicante; Cruz-Roja Central Hospital, Madrid; and Alcorcon Foundation-Hospital, Madrid) in 2007 and 2008.

Inclusion criteria. Patients aged 14–80 years with a diagnosis suggestive of NSAID reactions. The procedure for establishing the diagnosis is described below.

Exclusion criteria. Patients younger than 14 years and older than 80 years of age; patients with a suspicion or evidence of hypersensitivity reactions such as fixed drug eruption, erythema multiforme, Stevens–Johnson–TEN complex or acute exanthematic pustulosis; patients with chronic urticaria or acute recurrent urticaria not attributed to NSAID intake; pregnant or breastfeeding patients; patients taking beta-blockers or ACE inhibitors or with contraindications for epinephrine administration; patients who had acute infections and/or underlying cardiac, hepatic or renal diseases that contraindicated drug provocation tests (DPT); subjects with psychosomatic disorders; patients with one or more reactions to one NSAID with unknown tolerance to others; and patients who tolerated NSAIDs.

Patient classification. Patients who experienced at least two episodes with two or more different NSAIDs were classified as CI. Patients who had at least two episodes with the same NSAID and good tolerance to a strong COX inhibitor and/or evidence by *in vivo* tests supporting specific IgE antibodies or a T cell response to the drug were classified as SR.

The study was conducted according to the principles of the Declaration of Helsinki and approved by the Ethics Committees of each participating hospital. 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 (SPT) and measurement of total IgE in serum samples. Data were compared with a matched control group of 300 subjects who tolerated NSAIDs.

The clinical questionnaire included questions on nasal and bronchial symptoms: sneezing, itching, watery nose, nasal blockage, difficulty breathing, cough and wheezing. It also included symptoms attributed to food, hymenoptera stings or exposure to latex or metals, such as urticaria, angio-oedema, oral allergy syndrome, eczema, anaphylaxis or shock.

Table 1. Doses of NSAIDs used in challenges

Drug	(A) Doses used in challenges in suspected or confirmed CI The doses were administered at 90-min intervals (total accumulated dose)	(B) Doses used in challenges in suspected or confirmed SR The doses were administered at 90-min intervals (total accumulated dose)
Paracetamol	50, 100, 350, 500 mg (1000 mg)	5, 50, 100, 350 mg (500 mg)
Piroxicam	5, 15 mg (20 mg)	5, 5, 10 mg (20 mg)
Diclofenac	12.5, 12.5, 25 mg (50 mg)	5, 15, 30 mg (50 mg)
Dipyrone	50, 100, 150, 300 mg (575 mg)	1st day: 5, 10, 50 mg 2nd day: 50, 150, 300 mg (575 mg)
Ibuprofen	150, 150, 300 mg (600 mg)	5, 50, 100, 200, 250 mg (600 mg)
Indomethacin	10, 20, 20 mg (50 mg)	5, 5, 15, 25 mg (50 mg)
ASA	50, 100, 150, 250 mg (500 mg)	1st day: 5, 30, 100 mg 2nd day: 150, 300 mg (500 mg)

(A) Doses used in challenges in suspected or confirmed CI. (B) Doses used in challenges in suspected or confirmed SR.

AlA, aspirin-induced asthma; CI, cross-intolerance; SR, selective responders; NSAIDs, non-steroidal anti-inflammatory drugs.

The SPT was performed with a battery of 30 common inhalant allergens, including pollens, house dust mites, moulds and animal danders (ALK, Madrid, Spain). Histamine hydrochloride 10 mg/mL and phenolated glycerolsaline were used as positive and negative controls, respectively. A positive SPT response was defined as a weal diameter of 3 mm or larger to at least one of these aeroallergens. 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 ≥ 130 IU/mL was used to classify the subjects as atopic or non-atopic.

Skin testing

Prick testing and intradermal test (ID) were carried out as described [15] in patients with immediate reactions due to dipyrone compatible with SR using metamizol at 400 mg/mL for SPT and at 40 mg/mL for ID. An increase in the diameter of the weal area > 3 mm 20 min after testing was considered positive.

For clinical symptoms compatible with non-immediate SR, patch tests were made by mixing powdered drug in petrolatum at a concentration, as indicated: naproxen 5% w/w, diclofenac 1% w/w, dipyrone 10% w/w and etofenamate 1% w/w. The occlusion time was 48 h. Erythema with oedema, papules, vesicles or bullae 48 and/or 72 h after testing were considered positive [15].

Oral drug provocation test

This was performed in a single blind procedure. On the first day, placebo capsules were given at different times and on the second day (at least 1 week later) increasing doses of NSAIDs were administered orally at intervals of 90 min up to a total of two to four administrations, 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 (PEF) rate or hypotension] appeared, the procedure was stopped and the symptoms were evaluated and treated. If no symptoms appeared during drug administration, the therapeutic dose was achieved. If good tolerance occurred, a therapeutic course of 2 days was given 24 h afterwards. All drugs were given in opaque capsules prepared by the hospital pharmacy service.

If patients reported two or more episodes to different NSAIDs, they were classified as CI and alternative drugs such as paracetamol and piroxicam were tested, provided they were not involved in the reactions.

If patients reported one or more episodes to the same drug and tolerance to other NSAIDs was not known, the order of the challenge drugs was as follows: etoricoxib, paracetamol, piroxicam, ibuprofen, indomethacin and ASA. The whole sequence was not always followed in all cases. In those cases where ibuprofen was the imputed drug, diclofenac was administered, and vice versa. Once a positive response appeared, the procedure was stopped. If negative, the procedure was continued with the next non-involved drug. In cases of indomethacin involvement, ASA was given, and vice versa (see Fig. 1). If tolerance to the alternatives, including strong NSAIDs, was finally achieved, the patient was suspected to be a SR and the drug considered to be involved was given. Exceptions were severe reactions (anaphylaxis or anaphylactic shock) and patients who reported two or more clear episodes with the same drug. This protocol enabled us to classify patients not only as SR or CI but also to verify tolerance to different NSAIDs according to the potency of COX inhibition. If only one drug was involved with good tolerance to a strong COX inhibitor, patients were classified as SR. When one or more drugs were involved and there was a positive response to an alternative drug, patients were considered to have CI.

As described above, DPT was not performed with the culprit drug in patients with severe reactions (anaphylaxis or anaphylactic shock), and if they reported only one severe episode they were excluded from this study.

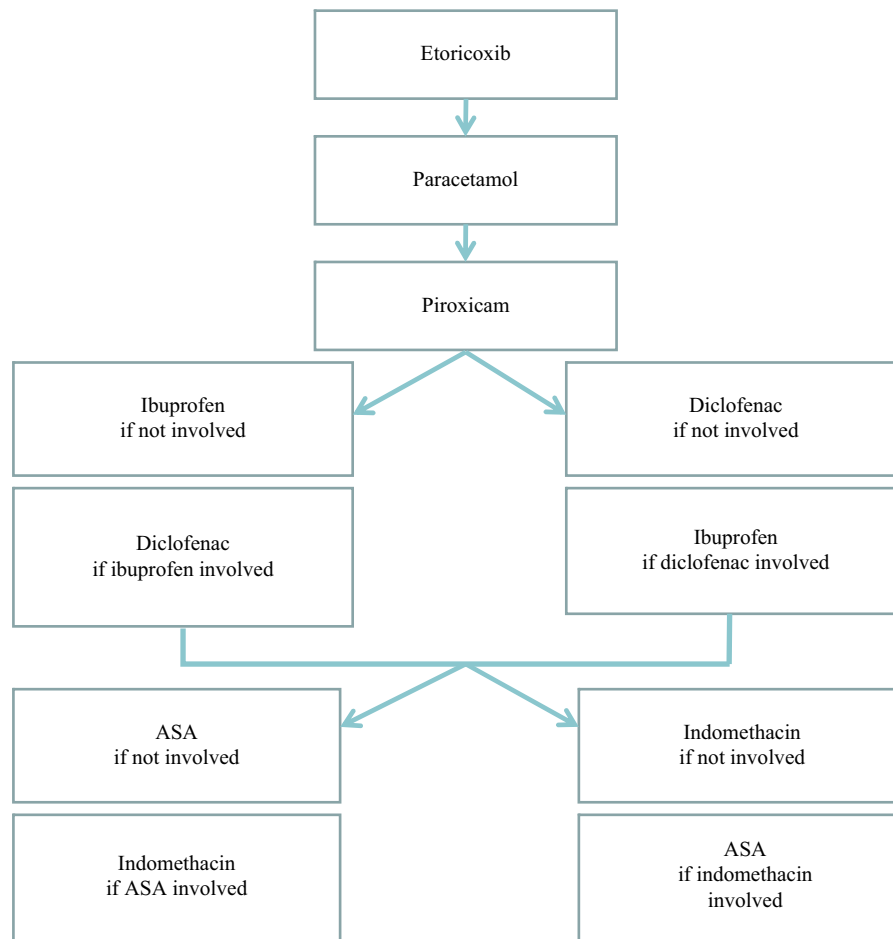


Fig. 1. Diagram for challenge procedure.

For cases of suspected CI, the dose escalation is shown in Table 1A. For cases suspected of having a severe reaction (CI) or to be SR, we used the dose escalation shown in Table 1B.

In all cases, symptoms attributed to the drug had to occur at least 1 month before performing the controlled oral challenge. Forced expiratory volume in 1 s values had to be at least 80% of predicted values, with an absolute value > 1.5 L. Hourly measurements of PEF with a mini-Wright peak flow meter (Clement Clarke International Ltd, London, UK) performed on the day before challenge showed a variability of <20% in PEF values in all subjects. Antihistamine agents were stopped 1 week before the challenge.

Nasal aspirin provocation test

In cases with respiratory involvement, if only one episode occurred, a controlled nasal challenge was carried out as described [16] in order to verify CI. The response to the nasal challenge was assessed by clinical symptoms and acoustic rhinometry, as described [17].

Statistical analysis

Data analysis was performed with the statistical package SPSS 15.0 for Windows (SPSS Inc., Chicago, IL, USA). χ^2 analysis was used to test differences for nominal variables and *t*-tests were used for interval variables with two groups. A *P*-value of <0.05 was considered statistically significant. The analysis included age, gender and the atopy status of patients and controls, number of episodes, clinical manifestations and drug involved in the reactions. For atopy, analysis was carried out considering one criterion (SPT to inhalant allergens) and the combination of two (SPT to inhalant allergens plus clinical symptoms) and three criteria (SPT to inhalant allergens plus clinical symptoms and total IgE > 130 IU/mL).

Results

The study included 659 patients who fulfilled the inclusion criteria and attended the clinics because of symptoms suggestive of hypersensitivity reactions after NSAID intake. Of these, 503 (76.3%) were classified as being CI and

156 (23.7%) as SR; 64.3% were women and 35.7% men, with a mean age of 41.7 ± 15.8 (14–80) years. No differences were found in sex or age between the CI and SR groups.

After skin testing, 302 (60%) of the CI group were considered to be atopic, with significant differences compared with the control group, where 124 (41.4%) were atopic ($P < 0.005$). This significant difference was also detected for total serum IgE. No differences were detected comparing the CI with the immediate SR group, due to the small number of SR. In CI, the most significant association was detected for positive skin prick testing to *Dermatophagoides farinae*, followed by *Dermatophagoides pteronyssinus* and dog dander (see Table 2A). No differences were found in prevalence with pollen allergens (*Lolium* and *Olea*). When this analysis was repeated after subclassifying CI patients according to skin, respiratory or skin plus respiratory involvement, no differences were found in the CI group with airway involvement (see Table

2B). No differences were found in age in these three groups.

Analysis of the combination of two criteria for atopy (SPT to inhalant allergens plus clinical entities) detected significant differences between CI and SR (the percentage of positives was 52% and 25% for CI and SR, respectively) and the control group (see Table 3, top part). Analysis of the three criteria (SPT to inhalant allergens plus clinical symptoms and total IgE > 130 IU/mL) only showed significant differences between CI and the control group (see Table 3, top part).

Comparison between the various clinical entities showed significant differences with rhinitis, asthma and food allergy when comparing CI and SR with the control group. The prevalence of other allergies, such as atopic dermatitis, hymenoptera allergy and latex allergy, was not compared because of the low number of patients.

The CI patients reported an average of 3.07 ± 2.005 (1–15) episodes after taking NSAIDs. This figure was

Table 2A. Atopic status in CI, immediate SR and control groups after skin prick test to common aeroallergens in our environment and total IgE in serum

	CI n (%)	Immediate SR n (%)	Control n (%)	P CI-SR	P CI-contr	P SR-contr
Positive skin tests						
<i>Lolium</i>	96 (19.1)	17 (22.6)	51 (17.2)	NS	NS	NS
<i>Cupressus</i>	44 (8.7)	0 (0)	7 (2.3)	NS	0.05	NS
<i>Olea europea</i>	107 (21.3)	7 (22.6)	58 (19.5)	NS	NS	NS
<i>Dermatophagoides pteronyssinus</i>	184 (36.6)	12 (16.1)	69 (23)	0.02	0.02	NS
<i>Dermatophagoides farinae</i>	178 (35.5)	7 (9.7)	62 (20.7)	0.004	0.01	NS
<i>Blomia tropicalis</i>	33 (6.6)	2 (3.2)	10 (3.4)	NS	NS	NS
<i>Alternaria</i>	27 (5.5)	0 (0)	3 (1.1)	NS	NS	NS
Dog dander	63 (12.6)	2 (3.2)	14 (4.6)	NS	0.04	NS
Cat dander	71 (14.2)	2 (3.2)	28 (9.2)	NS	NS	NS
At least one allergen	302 (60)	32 (41.9)	124 (41.4)	NS	0.005	NS
Total IgE in serum ≥ 130 IU/mL	168 (33.4)	12 (7.6)	20 (6.6)	NS	0.0001	NS

NS, no statistical difference; CI, cross-intolerance; SR, selective responders.

Table 2B. Atopic status in CI with skin, respiratory and skin plus respiratory involvement, after skin prick test to common aeroallergens compared with the control group

	CI Skin n (%)	CI Respiratory n (%)	CI Skin + airway n (%)	P SkinCI-cont	P RespCI-contr	P MixCI-cont
Positive skin tests						
<i>Lolium</i>	51 (16.2)	10 (16.6)	38 (29.2)	NS	NS	NS
<i>Cupressus</i>	31 (9.8)	0 (0)	14 (10.7)	0.03	NS	0.03
<i>Olea europea</i>	75 (23.8)	5 (8.3)	29 (22.3)	NS	NS	NS
<i>Dermatophagoides pteronyssinus</i>	129 (41)	13 (21.5)	46 (35.4)	0.007	NS	NS
<i>Dermatophagoides farinae</i>	123 (39.1)	13 (21.5)	46 (35.4)	0.005	NS	NS
<i>Blomia tropicalis</i>	25 (7.9)	0 (0)	9 (6.9)	NS	NS	NS
<i>Alternaria</i>	14 (4.4)	0 (0)	14 (10.7)	NS	NS	0.009
Dog dander	33 (10.5)	8 (13.2)	23 (17.7)	NS	NS	0.01
Cat dander	45 (14.3)	5 (8.3)	23 (17.7)	NS	NS	NS
At least one allergen	202 (64.3)	18 (29.8)	75 (57.7)	0.0001	NS	NS

NS, no statistical difference; CI, cross-intolerance.

Table 3. Comparison of atopic status in CI, immediate SR and control groups according to one, two or three criteria

	CI <i>n</i> (%)	SR <i>n</i> (%)	Control <i>n</i> (%)	<i>P</i> CI-SR	<i>P</i> CI-control	<i>P</i> SR-control
Atopy criteria						
Prick positive to at least one inhalant allergen	302 (60)	32 (41.9)	124 (41.4)	NS	0.005	NS
Prick+clinical symptoms	263 (52.3)	19 (25.8)	18 (6)	0.006	0.0001	0.003
Prick+clinical symptoms+IgE > 130 IU/mL	67 (13.3)	5 (6.8)	4 (1.2)	NS	0.01	NS
Entity						
Rhinitis	119 (23.65)	15 (20.27)	26 (8.53)	NS	0.0001	0.004
Asthma	72 (14.31)	6 (8.1)	3 (1)	NS	0.0001	0.0001
Food allergy	30 (5.96)	2 (2.7)	1 (0.34)	NS	0.0001	0.04
Latex allergy	2 (0.39)	0	0	NS	NS	NS
Hymenoptera allergy	2 (0.39)	0	0	NS	NS	NS
Atopic dermatitis	5 (0.99)	0	1 (0.34)	NS	NS	NS

We also analysed the clinical entities in the three groups.

NS, no statistical difference; CI, cross-intolerance; SR, selective responders.

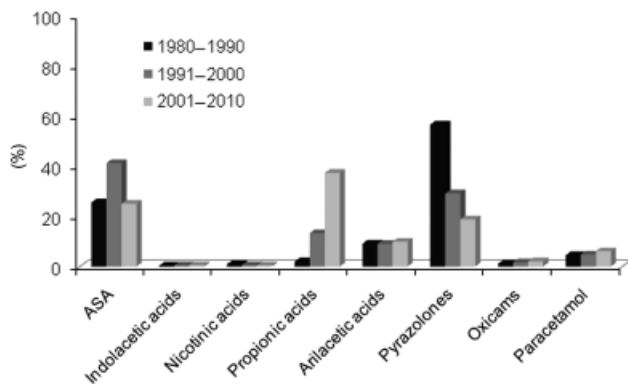


Fig. 2. Drugs involved in reactions induced by non-steroidal anti-inflammatory drugs in different periods of time. ASA, aspirin-sensitive asthma.

significantly higher compared with the SR patients (1.95 ± 1.13 , 1–6; $P < 0.0001$).

An analysis of the involvement of the different NSAIDs over a period of three decades is shown in Fig. 2. In the first decade (1980–1990), pyrazolones and ASA were the drugs most frequently involved in hypersensitivity reactions to NSAIDs. In the second decade (1991–2000), ASA was the most frequent and pyrazolones decreased. Propionic acid derivatives experienced a very important increase, rising from 2% in the first period to 37.3% in the third decade. Table 4 shows the drugs inducing episodes. In 36.56% of the CI patients, the reaction was induced by propionic acid derivatives, followed by aspirin (24.68%) and pyrazolones (18.19%). Paracetamol induced the response in 8.16% of the CI patients. On the other hand, pyrazolones were the most frequent drugs involved in SR (44.61%), followed by propionic acid derivatives (25.76%).

The analysis of the time interval between drug administration and symptom appearance is shown in Tables 5A and 5B. Most of the CI cases experienced the episode

Table 4. Drugs involved in reactions induced by NSAIDs reported by patients diagnosed as CI and SR

NSAIDs	CI <i>n</i> (%)	SR <i>n</i> (%)	<i>P</i>
ASA	293 (24.68)	22 (8.46)	0.0001
Indolacetic acid	6 (0.5)	0 (0)	ND
Nicotinic acid	7 (0.58)	0 (0)	ND
Arylacetic acid	105 (8.84)	33 (12.69)	ND
Propionic acid	434 (36.56)	67 (25.76)	0.001
Pyrazolone	216 (18.19)	116 (44.61)	0.0001
Oxicam	29 (2.44)	2 (0.7)	ND
Paracetamol	97 (8.16)	20 (7.69)	ND

AIA, aspirin-induced asthma; CI, cross-intolerance; SR, selective responders; NSAIDs, non-steroidal anti-inflammatory drugs.

within one hour of drug administration, followed by 20% who had the reaction within 1–6 h (see Table 5A). Only a minimum proportion of the CI cases experienced their reaction after an interval of more than 6 h. No differences in the time intervals were observed considering atopic vs. non-atopic patients. The same approach was made for the SR patients (see Table 5B). We found no significant differences in time interval after sub-classifying these patients into atopic and non-atopic patients.

In most patients, the symptoms reported after NSAID intake were limited to the skin, with urticaria being the most frequent manifestation in CI and SR. Symptoms of respiratory airway involvement and skin plus airway involvement were significantly more frequent in CI, whereas anaphylaxis was more frequent in SR. These differences were statistically significant (see Table 6). Of particular interest is the finding of three SR cases with airway involvement (one asthma, one rhinitis and one rhinitis plus asthma). Two cases developed two episodes each, one patient with paracetamol and the other with

Table 5A. Time intervals (and subdivision) between drug administration and appearance of reaction according to the patient report

Time interval (h)	CI <i>n</i> (%)	Time interval (h)	CI	
			Atopic patients <i>n</i> (%)	Non-atopic patients <i>n</i> (%)
< 1	235 (46.7)	< 1	164 (66.6)	71 (53.4)
1–6	106 (21)	–	–	–
6–24	38 (7.5)	≥ 1	82 (33.4)	62 (46.6)
Not recorded	124 (24.7)			

We compared atopic and non-atopic patients. No differences were found in either CI or SR. Time intervals between drug administration and appearance of reaction in CI patients.

CI, cross-intolerance; SR, selective responders.

Table 5B. Time intervals (and subdivision) between drug administration and appearance of reaction according to the patient report

Time interval (h)	SR <i>n</i> (%)	Time interval (h)	SR	
			Atopic patients <i>n</i> (%)	Non-atopic patients <i>n</i> (%)
< 1	74 (47.4)	< 1	32 (61.5)	42 (64.6)
1–6	33 (21.2)	–	–	–
6–24	10 (6.4)	≥ 1	20 (38.5)	23 (35.4)
Not recorded	39 (25)			

We compared atopic and non-atopic patients. No differences were found in either CI or SR. Time intervals between drug administration and appearance of reaction in SR patients.

CI, cross-intolerance; SR, selective responders.

Table 6. Symptoms reported by patients after NSAID intake. We compared the CI and SR groups.

Symptoms reported by patients after NSAID intake	CI <i>n</i> (%)	SR <i>n</i> (%)	<i>P</i>
Urticaria + angio-oedema	311 (61.8)	73 (46.8)	0.0001
Non-urticarial rash	1 (0.2)	6 (3.9)	0.0001
Eczema	2 (0.4)	1 (0.6)	ND
Asthma	38 (7.5)	1 (0.6)	0.008
Rhinitis	6 (1.2)	1 (0.6)	ND
Rhinitis + asthma	6 (1.2)	1 (0.6)	ND
Glottis oedema	10 (1.9)	0	ND
Anaphylaxis	36 (7.1)	66 (42.3)	0.0001
Skin + airways	93 (18.2)	7 (4.6)	0.0001

We compared the CI and SR groups.

NSAIDs, non-steroidal anti-inflammatory drugs; CI, cross-intolerance; SR, selective responders.

ibuprofen, and both were negative after provocation with ASA; and in the third case, ASA was the drug involved and a positive nasal challenge with L-ASA was found. Good tolerance to indomethacin existed in this case.

Prick tests were performed with dypirone, as described in the methods section, in the 33 patients with immediate reactions to this drug, with nine patients proving positive. One patient had a systemic reaction after SPT. In patients with a negative SPT, we carried out ID tests, with 13 patients being positive to dypirone. In patients with non-immediate reactions, patch tests were performed, as

described in the methods section. These were positive to naproxen and dypirone in one patient each and to etofenamate in five patients.

Fourteen CI patients had only one episode of respiratory involvement after NSAID intake. A controlled nasal challenge was carried out with L-ASA. This was positive in two patients (one asthma, and one rhinitis and asthma). In the remaining 12 patients, nasal challenge could not be completed because of the positive response to the control saline (false positive response). In these, an oral challenge was carried out. Four patients responded to an

Table 7. Challenges performed in both CI and SR groups.

Drug used in challenge	CI		SR		P
	Positive	Negative	Positive	Negative	
ASA	23	0	4	137	0.0001
Indomethacin	0	0	0	12	NA
Diclofenac	6	0	4	8	0.03
Ibuprofen	0	0	10	37	NA
Dypirone	0	0	3	1	NA
Piroxicam	28	131	0	129	0.0001
Paracetamol	32	341	8	112	ND
Etoricoxib	25	90	0	0	NA

ASA, aspirin-sensitive asthma; CI, cross-intolerance; SR, selective responders.

accumulative dose of 50 mg of ASA and eight patients to an accumulative dose of 150 mg of ASA.

A total of 676 oral challenges were performed in 503 CI patients and 465 in 156 SR patients. A mean of 1.71 ± 0.73 oral challenges were performed in the CI and 2.93 ± 1.11 in the SR.

In the CI group, DPT was needed to establish the diagnosis in 46 (9.1%) patients, whereas in 457 (90.9%) patients diagnosis was achieved by clinical history and DPT. As can be seen in Table 7, positive responses to paracetamol also occurred in this group. In order to verify the consistency with the clinical history, a representative sample of 50 CI patients diagnosed by clinical history underwent DPT with one of the culprit drugs, all of whom experienced the same symptoms as reported previously in the clinical history.

Discussion

The great world-wide use of NSAIDs [18] has resulted in this group of drugs being responsible for many adverse drug effects, including hypersensitivity reactions [1, 19]. In addition to aspirin, other NSAIDs, such as ibuprofen, are now taking on a predominant role [10, 19]. Here, we describe the drugs involved in reactions induced by NSAIDs over a consecutive period of 30 years, divided into three decades (Fig. 2). At the time the patients were included in this study, all the drugs were already available for prescription. Only COX-2 inhibitors were introduced in 2002 [20].

In the first decade (1980–1990), pyrazolones and ASA were the drugs most frequently involved in hypersensitivity reactions to NSAIDs; in the second decade (1991–2000), ASA was the most frequent and pyrazolones decreased; and in the third decade (2001–2010), propionic acid derivatives were the most frequent, with ASA the second and pyrazolones the least common. This may reflect the change in the consumption of each NSAID over time although no specific calculation of the consumption

in each period was known to be available at the time of this study. In latter years, the increased consumption of propionic acid derivatives has resulted in increasing reports of adverse effects to these compounds, such as gastrointestinal symptoms, asthma, renal failure, acute myocardial infarction and heart failure [21, 22], as well as hypersensitivity reactions [19, 23, 24].

Early studies of NSAID hypersensitivity reactions due to CI focused on respiratory airway involvement, including asthma and/or rhinitis and nasal polyposis [7, 25], though urticaria and anaphylaxis were also reported [2, 9, 10, 26, 27]. Over the years, anaphylactic reactions have frequently been reported in the emergency services [27]. Our data indicate that the skin is the most common organ affected in both CI and SR groups, as supported by other studies [10, 19, 28]. However, more studies are required in order to determine the prevalence of this phenomenon.

Studies have associated the response to NSAIDs with the exacerbation of urticaria and/or angio-oedema [2, 29]. In fact, subjects with urticaria and/or angio-oedema induced by NSAIDs may develop skin symptoms later in the course of the disease. Asero evaluated a group of 121 patients with multiple NSAID intolerance with no pre-existing urticaria over a variable period of 1–10 years after the first visit, estimating that 30% of patients developed urticaria in the absence of any trigger. In some cases, CI may precede the appearance of urticaria by years [29]. In our study, these patients were excluded, in order to avoid interference with pre-existing urticaria. Whether our group of patients will develop urticaria at some time in the future cannot be answered and requires a follow-up evaluation.

In most CI patients, the diagnosis was achieved by clinical history, with challenge only being needed in a very few. In order to verify the consistency of the criteria established in this study, a representative sample of 50 CI patients diagnosed by clinical history underwent DPT with one of the culprit drugs; they all experienced the same symptoms as those reported previously in their clinical history. Thus, challenge may be needed to find an alternative drug for these patients but is not strictly necessary to achieve the diagnosis when sufficient information is provided by the clinical history. In most SR patients, however, DPT with a strong COX-1 inhibitor was needed to achieve the diagnosis. However, challenge was only made in cases that were not severe, and the value of SR may be a little higher because only 11% of SR was severe.

We studied the association in the CI and SR groups between atopy and NSAID sensitivity by analysing skin test results, total IgE and the clinical history as compared with a matched control group with NSAID tolerance. Results showed that atopy was more common in CI patients, with a frequency of skin test positivity of 60% compared with 41.4% in the control group, confirming

other results [26, 28]. In this study, an association was observed between inhalant allergens and CI to NSAIDs, as reported elsewhere [26, 28, 30, 31]. Whether an association exists with food allergens was not assessed in this study. No differences were found in the SR group compared with the CI and control groups. When we analysed the CI patients sub-classified according to the organs involved, differences were only detected in patients with skin involvement, whether or not they also had respiratory symptoms. The reason for this is unknown. No differences were found in the percentage of atopy between the CI and SR patients, although the low number of cases with SR prevents statistical comparison.

As the mechanism determining the association between NSAID intolerance and atopy is currently unknown, increasing interest is being shown in performing genetic studies to attempt to clarify these mechanisms. Several authors have shown an association between atopy and CI to NSAIDs [26, 28, 30, 31]. Atopic genes implicated in IgE-allergic reactions include IL-4, IL-5 and IL-13, all localized in the same chromosomal region as the LTC4S gene, and cysteinyl leukotriene has been shown to enhance the production of IgE and IgG antibodies by B-lymphocytes [32–34]. Further studies are in progress by our group in order to attempt to determine this association more clearly.

Summarizing, after studying a large series of cases with hypersensitivity reactions to NSAIDs, we conclude that

cutaneous hypersensitivity reactions by CI to NSAIDs are the most frequent entities induced by these compounds, and that new drugs in this group are taking over from ASA as relevant triggers. The consistency of the criteria used to establish the diagnosis was validated by an appropriate oral-controlled challenge in a representative number of cases. The association between atopy and CI opens new paths for investigating the mechanisms involved in hypersensitivity reactions due to CI to NSAIDs.

Acknowledgements

We thank Ian Johnstone for help with the final English language version of the manuscript. J. A. Cornejo-García received a postdoctoral grant from the Alfonso Martin Escudero Foundation (Madrid, Spain). This study was supported by grants from the Spanish Health Ministry Fund for Health in Spain (FIS) network RIRAAF (RD07/0064), PI071220, PS09/02419 and PS09/00943. J. A. Cornejo-García received a postdoctoral grant from the Alfonso Martin Escudero Foundation (Madrid, Spain).

Conflict of interest: None of the authors has any conflict of interest. None has received any 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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