Hypersensitivity reactions to arylpropionic acid derivatives: different drugs inducing different response patterns

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Abstract

Background: Although ibuprofen and other arylpropionic acid derivatives (APs) are among the non-steroidal anti-inflammatory drugs (NSAIDs) most consumed worldwide at all age ranges, little is known about hypersensitivity to this group of drugs. Our aim was to characterise in detail patients reporting hypersensitivity reactions induced by APs. Methods: We prospectively evaluated patients with symptoms suggestive of hypersensitivity to APs and analysed their clinical characteristics, the reported reactions, and the diagnosis approach. Results: A total of 662 patients confirmed as hypersensitive to APs were included: 489 as cross-reactive (CR) hypersensitivity type (73.86%) and 173 as selective responders (26.13%) (SR). The percentage of subjects reporting reactions induced by ibuprofen and dexketoprofen was higher in CRs (p=0.005 and p=0.01, respectively), whereas reactions induced by naproxen and ketoprofen were more frequent in SRs (p=0.0002 and p=0.00001, respectively). The most frequent symptoms induced by ibuprofen, dexketoprofen, and naproxen were isolated angioedema and urticaria combined or not with angioedema in both NIUA and SNIUAA. NPT-LASA was positive in 156 cases (77.14% of NERD and 68.18% of blended) and DPT to ASA was needed in 246 (50.3%) CR patients. In 28 SR cases (25 SNIUAA and 3 SNIDR), DPT with the culprit AP was required. Conclusions: Skin is the most common organ involved in hypersensitivity to APs, in both CR and SR, with ibuprofen and dexketoprofen inducing most frequently CRs, and naproxen and ketoprofen SRs. More studies are needed to clarify the underlying mechanism in DHR induced by APs.

INTRODUCTION

Non-steroidal anti-inflammatory drugs (NSAIDs) are among the most widely used drugs in clinical practise worldwide [1]. This may contribute to them being the main triggers of drug hypersensitivity reactions (DHRs) [2].

The latest classification of NSAID-hypersensitivity proposed by the European Academy of Allergy and Clinical Immunology (EAACI) differentiates between cross-reactive type hypersensitivity (CRs) and selective reactions (SRs) [3]. The first one is the most frequent (up to 75%) in all age groups [4, 5], with patients reacting to NSAIDs from different chemical groups without specific immunological recognition, and which have been linked to COX-1 inhibition in susceptible individuals. In SRs, patients react to one or more

NSAIDs from the same chemical group through a specific immune mechanism (IgE or T cell mediated) while tolerating other non-chemically related NSAIDs [3].

CRs to NSAIDs induce at least three clinical entities [3]: a) NSAIDs-exacerbated respiratory disease (NERD), in patients with underlying rhinitis and/or asthma with or without nasal polyposis; b) NSAIDs-exacerbated cutaneous disease (NECD), in patients with underlying chronic spontaneous urticaria (CSU); and c) NSAIDs-induced urticaria/angiodema (NIUA), in otherwise healthy individuals, being the most frequent clinical entity and also the most frequently induced by hypersensitivity to drugs [2]. SRs include: single-NSAID-induced urticaria/angioedema and anaphylaxis (SNIUAA), in which the reaction appears within seconds to the first hour after taking the NSAID; and single-NSAID-induced delayed reactions (SNIDRs), in which patients develop a reaction from 24 hours to days or weeks after the intake of a NSAID [3].

However, this classification does not take into consideration some entities that are frequently observed in clinical practice. One of them is blended reactions, with simultaneous cutaneous and respiratory manifestations [4, 6-8], which account for more than 25% of the total DHRs to NSAIDs [8]. They are probably not identified as such and classified as NERD or NIUA, or they may be even confused with anaphylactic (IgE-mediated) reactions. These facts have important consequences for the patient, as all NSAIDs may be avoided and other therapeutic alternatives used unnecessarily.

The diagnosis approach of DHRs to NSAIDs is complex as there are no useful in vitro methods and skin tests are only applicable for pyrazolones. Therefore, diagnosis usually relies on a compatible clinical history and, in many cases, also on drug provocation test (DPT) with the culprit NSAID, a test that represents a risk for the patient and a considerable consumption of resources [3, 4, 9]. Recently, some progress has been made regarding the management of DHRs to NSAIDs, highlighting the role of the nasal provocation test (NPT) with lysine acetylsalicylate (LASA) when airways are involved [4, 8, 10-14].

NSAIDs include a wide number of drugs with different chemical structures. Aryl-propionic derivatives (APs) are characterised by the presence of an asymmetrical carbon atom adjacent to a carboxylic acid and include a wide number of molecules: ibuprofen, loxoprofen, naproxen, ketoprofen, dexketoprofen, fenoprofen, flurbiprofen, indoprofen, tiaprofenic acid, and oxaprozin [15]. In Spain, only ibuprofen, flurbiprofen, naproxen, dexketoprofen, and ketoprofen are commercialised. Ibuprofen and other APs are among the most consumed NSAIDs worldwide [16]. In fact, in Spain they account for 65.1% of NSAID consumption [17]. However, despite their common consumption, the specific role of APs in DHRs to NSAIDs and the different clinical phenotypes they induce have not been defined. Therefore, our aim was to perform a detailed clinical characterisation of DHRs induced by ibuprofen and others APs through the analysis of the clinical history, the reported reactions, as well as the diagnostic approach used.

METHODS

Patients

We prospectively evaluated patients with symptoms suggestive of DHRs to NSAIDs who had been referred to the Allergy unit of the Hospital Regional Universitario de Málaga (Málaga), Hospital Clínic (Barcelona), Hospital Universitario Fundación Alcorcón (Madrid), and Hospital Regional Universitario de Ciudad Real (Ciudad Real) for a period of 13 years (2005-2018).

Inclusion criteria. Patients [?]14 years-old confirmed as having DHRs to APs.

Exclusion criteria. Patients <14 years-old; patients in whom the allergological study was not completed and therefore diagnosis as either DHRs or tolerant to NSAIDs could not be confirmed: pregnant or breast-feeding 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 DPTs; subjects with psychosomatic disorders; and subjects who refused the study.

Patient classification

Patients included were classified into two groups [10]: a) CRs, if they experienced 3 or more episodes of cutaneous and/or respiratory symptoms after the intake of at least 3 different non-chemically related NSAIDs, including a strong COX-1 inhibitor (acetylsalicylic acid, ASA); and b) SRs, if patients had at least two episodes after the intake of the same NSAID and tolerance to a strong COX inhibitor (ASA).

CR patients were sub-classified into: i) NERD, if patients with underlying rhinitis and/or asthma with or without nasal polyposis reported respiratory symptoms (rhinitis, asthma and/or glottis edema) after NSAID intake; ii) NECD, if patients with underlying CSU experienced exacerbation of skin symptoms (urticaria and/or angioedema, AE) after NSAID intake; iii) NIUA, if patients without underlying CSU had urticaria and/or angioedema after NSAID intake; iv) blended reactions, if patients had a combination of skin (urticaria and/or angioedema) and respiratory symptoms (rhinitis, asthma and/or glottis edema) after NSAID intake.

SR patients were sub-classified into: v) SNIUAA, if patients experienced urticaria, angioedema, or anaphylaxis within one hour up to 24 hours after NSAID intake; vi) SNIDR, in patients experienced cutaneous manifestations with or without systemic involvement more than 24 hours after NSAID intake [18].

Clinical history

Patients were asked about their reaction symptoms: skin [19] and respiratory (sneezing, itching, watery nose, nasal blockage, difficulty breathing, cough, and wheezing), the interval between NSAID intake and reaction onset, the number of episodes, the interval between their last reaction and the study, and the presence of other underlying diseases (rhinitis, asthma, food allergy, and CSU).

Atopic status

This was assessed by skin prick test (SPT) using a panel of 20 common inhalant allergens, including pollens, house dust mites, molds, and animal dander, and 27 common food allergens including animal, fruit, and vegetable allergens (ALK, Madrid, Spain). Histamine hydrochloride (10 mg/ml) and phenolated glycerol saline were used as positive and negative controls, respectively. Patients were requested to stop taking any antihistamine medication at least 8 days before undergoing SPT. A positive SPT response was defined as a wheal diameter of 3 mm or larger to at least one of these allergens; patients developing such a wheal were considered atopic.

Skin tests

For SNIDR, patch tests with the culprit AP were performed as described [20] with ibuprofen at 5% and 10%, dexketoprofen at 1% and 2%, naproxen at 5%, and ketoprofen at 1%, all of them in petrolatum [21, 22].

Nasal provocation test

NPT-LASA was performed in all patients reporting respiratory symptoms, regardless of the other organs involved [10, 23]. Results were considered positive if an increase [?]30% in the total nasal symptoms and a decrease [?]30% in the total volume of both nasal cavities from 2 to 6 cm (vol 2–6 cm), measured by acoustic rhinometry, was observed.

Drug provocation test

DPTs were performed in a single blind manner [9, 12-14, 24]: placebo capsules were given at different times on the first day; and increasing doses of NSAIDs were administered orally on the second/third days. The two/three test days were separated by at least 1 week. Drugs and placebo were given in opaque capsules prepared by the hospital pharmacy service.

DPT to ASA was performed in patients reporting less than 3 episodes induced by less than 3 different NSAIDs in order to classify them into CRs (they reacted to ASA) or SRs (they tolerated ASA) (Figure 1) [10]. For DPT, two doses of ASA were administered orally (50 and 100 mg) with an interval of 180 minutes on the 2nd day test. If negative, other two doses of ASA (250 and 500 mg) were administered on the 3rd day, also with a 180-minute interval.

In addition to ASA, DPT to the culprit AP was performed in subjects who tolerated ASA if they reported less than 2 episodes induced by APs [10, 18]. If they reacted, they were classified into SRs, whereas if they tolerated the culprit APs, they were confirmed as non-allergic (Figure 1) [10]. Drugs were given in increasing doses every 90 minutes: 5, 50,100, 200, and 250 mg for ibuprofen (accumulative dose 600 mg); 3.125, 3.125, 6.25, and 12.5 for dexketoprofen (accumulative dose 25 mg); 5, 10, and 50 mg in the second day and 50, 100, 100, 250 mg (accumulative dose 500 mg) in the third day for naproxen; and 5, 10, 10, and 25 mg for ketoprofen (accumulative dose 50 mg).

If cutaneous and/or respiratory symptoms or alterations in vital signs appeared, the procedure was stopped and the symptoms were evaluated and treated. If no symptoms appeared during DPT and the therapeutic dose was achieved, a 2-day/8-hour course of the therapeutic dose after a gap of 24 hours was performed [13].

Before beginning the DPT procedure, patients were stable and their forced expiratory volume in 1s had to be at least 80% of the predicted value, with an absolute volume of at least 1.5 L. Medications were stopped before DPT according to international guidelines [9, 12-14, 24].

Statistical analysis

Data analysis was performed using Chi-square analysis to test differences in nominal variables between groups, Fisher test was used when there were no criteria for using Chi-square test, and Mann-Whitney test was used for quantitative variables. All reported p values represented two-tailed tests, with values <0.05 considered statistically significant.

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

RESULTS

A total of 1612 patients with a clinical history suggestive of DHR to APs were prospectively evaluated in 4 Spanish centres. Among these, full diagnosis could be achieved in 662 patients: 489 were confirmed as CRs (73.86%) and 173 as SRs (26.13%). In 698 subjects the diagnosis of DHR was discarded as they tolerated the culprit AP in the allergological study, and in 252 the diagnosis of DHR or tolerance could not be achieved: 185 could not undergo DPT to the culprit due to age, comorbidities or because it was contraindicated due to the potential severity of the reaction; 65 did not give consent for the DPTs; and 2 were excluded due to pregnancy (Figure 2).

Clinical data of the subjects confirmed as DHR

The 662 subjects confirmed as of DHR to APs had a median age at diagnosis of 38 [interquartile range (IR): 26–49] years, and 402 (60.73%) were female. A total of 284 had underlying rhinitis (42.9%); 161 had asthma (24.32%); 61 had nasosinusal polyposis (9.21%); 49 CSU (7.4%), and 24 food allergy (3.63%) (3 to nuts, 7 to shellfish, 6 to melon, 5 to peach, 2 to apple, 1 to kiwi, and 1 to banana). The percentage of rhinitis, asthma, nasosinusal polyposis, and CSU was higher in CRs compared with SRs (Table 1). A total of 440 patients were atopic (66.46%), being most frequently detected sensitisations to *Dermatophagoides pteronyssinuss* (264; 39.87%), *Olea europaea* (217; 32.77%), and *Lolium perenne* (175; 26.43%) No differences were observed comparing CRs and SRs (Table 1 and Supplemmentary Table 1).

Patients confirmed as blended were the youngest (p=0.01), being the percentage of females higher in NERD and SNIDR (p=0.01). The percentage of cases with underlying rhinitis, asthma, and nasosinusal polyposis was higher in NERD cases, followed by blended cases ($p<0.0001$, respectively). The percentage of atopy was higher in NIUA, NECD, blended, and SNIUAA ($p<0.0001$), being the percentage of sensitisations to *D. pteronyssinus* higher in NIUA and SNIUAA (p=0.0003) and to Alternaria and Pru p 3 in blended ($p<0.0001$ and p=0.01, respectively) compared with the other clinical entities (Table 2 and Supplemmentary Table 2).

Cases reported a total of 1946 episodes induced by NSAIDs, being 1341 induced by APs, with a median of 2 [IR: 1-2] episodes induced by APs intake per patient, being the median higher in SRs compared with CRs

(2 [IR: 2-3] vs 1 [IR: 1-2]; p<0.0001). In most subjects (601; 90.78%), reported reactions were induced by ibuprofen, followed by dexketoprofen (96; 14.5%), naproxen (64; 9.66%), and ketoprofen (9; 1.35%). In 100 cases (73 CRs and 27 SRs), 2 different APs were involved in the reactions, and in 4 cases 3 different APs were reported, all of them CRs. Comparing CRs and SRs, the percentage of subjects reporting reactions induced by ibuprofen (CR: 453 (92.63%) vs SR: 148 (85.54%); p=0.005) and dexketoprofen (CR: 81 (16.56%) vs SR: 15 (8.67%), p=0.01) was higher in CRs, and patients reporting reactions induced by naproxen (CR: 37 (7.15%) vs SR: 29 (16.76%); p=0.0002) and ketoprofen (CR: 1 (1.84%) vs SR; 8 (4.62%); p=0.00001) were more frequent in SRs. All APs were administered orally, except for 27 cases in which dexketoprofen was administered by parenteral route (intravenous and intramuscular) and 6 cases in which ketoprofen were administered topically. In 147 cases confirmed as CRs, 605 episodes were induced by others NSAIDs different from APs: 180 (36.8%) cases reported reactions induced by pyrazolones (175 by metamizol and 5 by propifenazone), 164 (33.53%) by ASA, 82 (16.76%) by arylacetic acid derivatives (73 by diclofenac, 6 by ketorolac and 3 by aceclofenac), 66 (13.49%) by paracetamol, 9 (1.84%) by oxicams (7 by meloxicam and 2 by piroxicam), 5 (1.02%) by lysine clonixinate, 2 (0.4%) by etoricoxib, 2 (0.4%) by indomethacin, and 1 (0.2%) by nimesulide.

According to the clinical entity, a total of 225 cases were confirmed as NIUA (33.98%), 150 as SNIUAA (22.65%), 110 as blended (16.61%), 105 as NERD (15.86%), 49 as NECD (7.4%), and 23 as SNIDR (3.47%) (Figure 1). Ibuprofen and dexketoprofen induced NIUA more commonly than other APs (34.8%, p<0.0001; and 42.7%, p=0.02, respectively), whereas naproxen induced more frequently SNIUAA (34.4%, p=0.0004), and ketoprofen induced SNIDR (77.8%, p<0.0001) (Table 3).

The most frequent symptoms induced by ibuprofen, dexketoprofen, and naproxen were isolated AE and urticaria combined or not with AE in both NIUA and SNIUAA, and the most frequent ones induced by ketoprofen were contact eczema and maculopapular exanthema (MPE) in SNIDR (Table 4). No differences were found in the percentage of atopic patients comparing the clinical symptoms induced by each AP (data not shown).

The time interval between the AP intake and the onset of the reaction was shorter for NERD (30 [IR:15-50] minutes), blended (30 [IR: 10-60] minutes), and SNIUAA (30 [IR: 30-120] minutes, respectively) compared with NECD (60 [IR: 30-120] minutes), NIUA (60 [IR: 15-120] minutes) and SNIDR (2160 [IR: 510-7200] minutes) (p<0.0001). No differences were found comparing the APs involved in each clinical entity (data not shown).

Methods used for diagnosis

The median time interval between the reaction and the study was 150 days [IR: 60-365] with no statistically significant differences among the APs involved and the clinical entity (data not shown).

NPT-LASA was positive in 156 cases: 81 in NERD (77.14%) and in 75 cases confirmed as blended (68.18%) (Table 5). DPT to ASA was needed to establish the diagnosis in 246 CR patients (50.3%) as they had NPT-LASA negative and/or only one episode reported: 19 were NERD (18.09%), 37 NECD (75.51%), 166 NIUA (73.77%) and 24 blended (21.81%). In 87 CR cases (17.79%) the diagnosis was established by clinical history as they reported 3 or more unequivocal episodes induced by NSAIDs: 5 were NERD (4.76%), 12 NECD (24.48%), 59 NIUA (26.22%), and 11 blended (10%) (Table 5).

All SRs tolerated ASA in DPT. In 10 SNIDR cases (43.47%), patch test to the culprit was positive: 4 cases reporting contact eczema (3 induced by ketoprofen and 1 by dexketoprofen), 3 cases of fixed drug eruption (2 induced by naproxen and 1 by ibuprofen), 2 cases of MPE, and 1 case of AE induced by ketoprofen. In 125 SNIUAA (83.33) and 10 SNIDR (43.47%) patients the diagnosis was established by clinical history as they reported at least two unequivocal episodes induced by APs. However, in 28 SR cases (16.18%) DPT with the culprit was required as the patients reported only one episode induced by APs and patch tests were negative: 25 SNIUAA (16.66%) and 3 SNIDR (13.04%) (Table 5). No differences were found comparing the dose inducing the reaction and the positive response in DPT as well as the interval time between the last dose and the onset of both the reaction reported by patient and the one in a positive DPT, considering each

AP and each the clinical entity (data not shown).

DISCUSSION

NSAIDs, especially ibuprofen and other APs, are among the most widely used drugs in clinical practise for treating pain and different inflammatory conditions [1]. They are often available over the counter, and patients may obtain them without any medical supervision, which contributes to their high consumption. Thus, 57.8% of the Danish [25] and 43.6% of the French [26] general populations claimed at least one prescription for NSAIDs during the period 1997-2005 and 2009-2010, respectively; and 16.9% of children were exposed to at least one NSAID according to a population-based European study [27]. In addition, their consumption has been increasing over recent years. For example, in Spain the NSAID consumption has increased 26.5% from 2000 to 2012, mainly due to ibuprofen, whose use has multiplied by 4 over this period of time [17]. This high consumption may contribute to NSAIDs, especially ibuprofen and other APs, being the main triggers of DHRs [1, 2].

The most frequent type of DHR induced by APs is CR, as it has been described in general with NSAIDs [4, 5, 11]. Similarly, the most common clinical entity observed was NIUA, as other previous reports dealing with NSAIDs had described [4, 5, 11, 28, 29]. However, although all APs could potentially induce all types of reactions and clinical entities, analysing the APs involved in the reported reaction, we found that ibuprofen and dexketoprofen induced most frequently NIUA, whereas naproxen induced most commonly SNIUAA, and ketoprofen induced SNIDR. Nevertheless, the symptoms experienced by patients were most commonly isolated angioedema and urticaria in both NIUA and SNIUAA. It is not known the reason why different APs molecules induce similar clinical symptoms although the reactions are suspected to be mediated by different mechanisms: COX-1 inhibition related mechanism for NIUA and specific IgE mediated mechanism for SNIUAA [3, 11]. Atopy has been associated with CR induced by NSAIDs [4, 6, 11, 30], however, in our study no differences were found in the percentage of atopic patients in NIUA and SNIUAA induced by APs. A reason why naproxen induces more frequently SNIUAA could be the immunogenic potency of the naproxen molecule. In fact, analysing the cases in which the diagnosis was not confirmed (data not shown), naproxen induced the highest percentage of anaphylaxis compared with the others APs, thus the percentage of SNIUAA induced by naproxen may be higher than what we found. Moreover, ketoprofen has been implicated in SNIDR more frequently than other APs. It is known that ketoprofen is the main NSAID involved in contact dermatitis and this reaction seems to be reported more commonly with topical formulations, which may be due to the higher concentrations of the drug in the skin [31]. This reaction could be due to its chemical structure [31], however, like with others APs, the molecular basis of ketoprofen-induced DHR remains to be fully elucidated. Therefore, more studies are needed in other to achieve a better knowledge of the underlying mechanisms in DHRs induced by APs, which will also influence in a better diagnosis approach.

The most important issue in the diagnosis of DHRs to NSAIDs is the differentiation between CRs and SRs, as in the first group patients must avoid all NSAIDs while in the latter patients must avoid only the culprit. A diagnosis of CRs, whether confirmed or not, implies a great impact on the patient quality of life as therapeutic alternatives are highly reduced, especially in children [3]. Another relevant matter regarding diagnosis is that nowadays skin tests and in vitro tests are not available for all NSAIDs, including APs, being the gold standard DPT, a costly and risky procedure [9-11, 13, 14]. NPT-LASA is a faster and safer method than oral DPT that has demonstrated to be useful in the diagnosis of DHRs induced by NSAIDs when airways are involved [8, 12, 14]. In our study, we also found this technic useful in both NERD and blended cases induced by APs, allowing confirming the 77% and 68% of cases, respectively. This means that in a high percentage of cases we could avoid an oral DPT. However, when NPT-LASA are negative and when skin is the only organ involved, DPT is the only method available to achieve the diagnosis, and it is not always performed due the risks and costs. This implies that a considerable percentage of patients with an unconfirmed diagnosis, who could be SR or even non-allergic, are recommended to avoid NSAIDs, which reduces highly the therapeutic alternatives.

Summarising, APs are the most frequently NSAIDs involved in DHRs to NSAIDs, probably related to their

high consumption. Skin is the most common organ involved in DHRs induced by APs, in both CR and SR, with ibuprofen and dexketoprofen inducing most frequently CR, and naproxen and ketoprofen inducing SR. More studies are needed to clarify the underlying mechanism in DHR induced by APs.

Table 1 . Demographic and clinical characteristics of the patients included in the study. CR: Cross-reactive type hypersensitivity. NA Not applicable. SR: Selective reaction.

			CR n=489	SR n=173	p
Age; median (interquartile range) years	Age; median (interquartile range) years	Age; median (interquartile range) years	38 (26.25-49)	38 (26-49.25)	0.8391
Gender; n (%) female/ n (%) male	Gender; n (%) female/ n (%) male	Gender; n (%) female/ n (%) male	294 (60.1)/ 195 (39.9)	108 (62.4)/ 65 (37.6)	0.5936
Underlying diseases; n (%)	Underlying diseases; n (%)	Rhinitis	234 (47.9)	50 (28.9)	<0.0001
		Asthma	142 (29)	19 (11)	<0.0001
		Nasosinusal polyposis	60 (12.3)	1 (0.6)	<0.0001
		Food allergy	15 (3.1)	9 (5.2)	0.1967
		Chronic urticaria	49 (10.02)	-	NA
Atopy; n (%)	Atopy; n (%)	Atopy; n (%)	324 (66.25)	116 (67.05)	0.9254
Allergen sensitisations; n (%)	Grass pollen	Grass pollen	123 (25.15)	52 (30.05)	0.2087
	Cupressus pollen	Cupressus pollen	64 (13.08)	25 (14.45)	0.6515
	Olive pollen	Olive pollen	161 (32.92)	56 (32.36)	0.8938
	D. pteronysissnus	D. pteronysissnus	198 (40.49)	66 (38.15)	0.589
	Alternaria	Alternaria	62 (12.67)	20 (11.5)	0.7012
	Pru p 3	Pru p 3	39 (7.97)	15 (8.67)	0.7741

Table 2. Demograhic and clinical characteristics of the patients included in the study according to the clinical entity. NA: Not applicable. NECD: NSAIDs-exacerbated cutaneous disease. NERD: NSAIDs-exacerbated respiratory disease. NIUA: NSAIDs-induced urticaria/angioedema. SNIDRs: Single-NSAID-induced delayed reactions. SNIUAA: Single-NSAID-induced urticaria/angioedema and anaphylaxis.

			NERD n=105	NECD n=49	NIUA n=225	Blended n=110	SNIUAA n=150	SNIDR n=23	p
Age; median (interquartile range) years	Age; median (interquartile range) years	Age; median (interquartile range) years	41.5 (29-51.25)	44 (29-48)	39 (25-49)	33.5 (20-47)	37 (24-50)	42 (36-48.5)	0.0

			NERD n=105	NECD n=49	NIUA n=225	Blended n=110	SNIUAA n=150	SNIDR n=23	p
Gender; n (%) female/ n (%) male	Gender; n (%) female/ n (%) male	Gender; n (%) female/ n (%) male	76 (72.4)/ 29 (27.6)	33 (67.3)/ 16 (32.7)	119 (52.9)/ 106 (47.1)	66 (60)/ 44 (40)	91 (60.7)/ 59 (39.3)	17 (73.6)/ 6 (26.1)	0.0
Underlying diseases; n (%)	Underlying diseases; n (%)	Rhinitis	79 (75.2)	14 (28.6)	88 (39.1)	53 (48.2)	46 (30.7)	4 (17.4)	<0
		Asthma	74 (70.5)	3 (6.1)	25 (11.1)	40 (36.4)	18 (12)	1 (4.3)	<0
		Nasosinusal polyposis	49 (46.7)	-	2 (0.9)	9 (8.2)	1 (0.7)	-	<0
		Food allergy	3 (2.9)	1 (2)	6 (2.7)	5 (4.5)	9 (6)	-	0.5
		Chronic urticaria	-	49	-	-	-	-	NA
Atopy; n (%)	Atopy; n (%)	Atopy; n (%)	52 (49.52)	35 (71.42)	159 (70.66)	78 (70.9)	108 (72)	8 (34.78)	<0
Allergen sensitisations; n (%)	Grass pollen	Grass pollen	26 (24.76)	15 (30.61)	54 (24)	28 (25.45)	48 (32)	4 (17.39)	0.5
	Cupressus pollen	Cupressus pollen	6 (5.71)	2 (4.08)	34 (15.11)	22 (20)	21 (14)	4 (17.39)	0.0
	Olive pollen	Olive pollen	30 (28.57)	15 (30.61)	71 (31.55)	45 (40.9)	53 (35.33)	3 (13.04)	0.1
	D. pteronysissnus	D. pteronysissnus	28 (26.66)	17 (34.69)	114 (50.66)	39 (35.45)	61 (40.66)	5 (21.73)	<0
	Alternaria	Alternaria	8 (7.61)	3 (6.12)	19 (8.4)	32 (29.09)	17 (11.33)	3 (13.04)	<0
	Pru p 3	Pru p 3	9 (8.57)	-	14 (6.22)	16 (14.54)	15 (10)	-	0.0

Table 3. APs involved in the reported reactions according to the clinical entities. CR: Cross-reactive type hypersensitivity. NECD: NSAIDs-exacerbated cutaneous disease. NERD: NSAIDs-exacerbated respiratory disease. NIUA: NSAIDs-induced urticaria/angioedema. SNIDRs: Single-NSAID-induced delayed reactions. SNIUAA: Single-NSAID-induced urticaria/angioedema and anaphylaxis. SR: Selective reaction.

		CR	CR	CR	CR	SR	SR	P
		NERD n=105	NECD n=49	NIUA n=225	Blended n=110	SNIUAA n=150	SNIDR n=23	
Drug involved; n (%)	Ibuprofen	98 (16.3)	44 (7.3)	209 (34.8)	102 (17)	138 (23)	10 (1.7)	<0.0001
	Dexketoprofen	11 (11.5)	6 (6.2)	41 (42.7)	23 (24)	12 (12.5)	3 (3.1)	0.02

	CR	CR	CR	CR	SR	SR	P
Naproxen	5 (7.8)	1 (1.6)	19 (29.7)	10 (15.6)	22 (34.4)	7 (10.9)	0.0004
Ketoprofen	-	-	1 (11.1)	-	1 (11.1)	7 (77.8)	<0.0001
P	0.113	0.2858	0.1347	0.1757	0.009591	6.755e-12	

Table 4. APs involved in the reported reactions according to the symptoms experienced. Anaph: Anaphylaxis. Asth: Asthma. Cont. ecz: Contact eczema. CR: Cross-reactive type hypersensitivity. FDE: Fixed drug eruption. Isol. AE: Isolated angioedema. MPE: Maculopapular exanthema. NECD: NSAIDs-exacerbated cutaneous disease. NERD: NSAIDs-exacerbated respiratory disease. NIUA: NSAIDs-induced urticaria/angioedema. Rhin: Rhinitis. SJS: Steven-Johnson syndrome. SNIDRs: Single-NSAID-induced delayed reactions. SNIUAA: Single-NSAID-induced urticaria/angioedema and anaphylaxis. SR: Selective reaction. Urt: Urticaria. Urt±AE: Urticaria combined or not with angioedema.

	CR; n (%)	CR; n (%)	CR; n (%)	CR; n (%)	CR; n (%)	CR; n (%)	CR; n (%)	CR; n (%)	CR; n (%)	CR; n (%)	SR; n (%)	SR; n (%)	SR; n (%)	SR; n (%)	SR n (%
	NERD Rhin	NERD Asth	NECD Isol. AE	NECD Urt± AE	NIUA Isol. AE	NIUA Urt± AE	Blended Urt/ AE+ Rhin/ Asth	Blended Urt/ AE+ GE	Blended Urt/AE+ Rhin/ Asth+ GE	Blended GI + Urt/ AE /Rhin/ Asth/ GE	SNIUAA Isol. AE	SNIUAA Urt	SNIUAA Rhin/ Asth	SNIUAA Anaph	SN Ur
Ibuprofen n=601	17 (2.82)	81 (13.47)	16 (2.66)	28 (4.65)	100 (16.63)	109 (18.13)	63 (10.48)	23 (3.82)	7 (1.16)	9 (1.49)	55 (9.15)	50 (8.31)	4 (0.66)	29 (4.82)	2 (0
Dexketo-n n=96	4 (4.16)	7 (7.29)	1 (1.04)	5 (5.2)	20 (20.83)	21 (21.87)	10 (10.41)	9 (9.37)	3 (3.12)	1 (1.04)	6 (6.25)	3 (3.12)	-	3 (3.12)	-
Naproxen n=64	-	5 (7.81)	-	1 (1.56)	11 (17.18)	8 (12.5)	9 (14.06)	-	1 (1.56)	-	9 (14.06)	8 (12.5)	-	5 (7.81)	-
Ketopr. n=9	-	-	-	-	-	1 (11.11)	-	-	-	-	-	1 (11.11)	-	-	-

Table 5. Methods used to achieve diagnosis for each clinical entity. CR: Cross-reactive type hypersensitivity. NECD: NSAIDs-exacerbated cutaneous disease. NERD: NSAIDs-exacerbated respiratory disease. NIUA: NSAIDs-induced urticaria/angioedema. SNIDRs: Single-NSAID-induced delayed reactions. SNIUAA: Single-NSAID-induced urticaria/angioedema and anaphylaxis. SR: Selective reaction.

	CR	CR	CR	CR	SR	SR
	NERD n=105	NECD n=49	NIUA n=225	Blended n=110	SNIUAA n=150	SNIDR n=23
TPN-LASA; n (%)	81 (77.14)	-	-	75 (68.18)		
DPT to ASA; n (%)	19 (18.09)	37 (75.51)	166 (73.77)	24 (21.81)		

	CR	CR	CR	CR	SR	SR
DPT to the culprit; n (%)	-	-	-		25 (16.66)	3 (13.04)
Clinical history; n (%)	5 (4.76)	12 (24.48)	59 (26.22)	11 (10)	125 (83.33)	10 (43.47)
Patch test; n (%)						10 (43.47) Ibuprofen n=1 (FDE) Dexketoprofen n=1 (contact eczema) Naproxeno n=2 (FDE) Ketoprofen n=6 (Contact eczema n=3, MPE n=2, AE=1)

Legend to Figure 1. Algorithm carried out for establishing the diagnosis.

Legend to Figure 2. Flow chart of the patients evaluated due to DHR to Aps.

REFERENCES

1. Dona, I., et al., *Trends in hypersensitivity drug reactions: more drugs, more response patterns, more heterogeneity.* J Investig Allergol Clin Immunol, 2014.**24** (3): p. 143-53; quiz 1 p following 153.

2. Dona, I., et al., *Drug hypersensitivity reactions: response patterns, drug involved, and temporal variations in a large series of patients.* J Investig Allergol Clin Immunol, 2012. **22** (5): p. 363-71.

3. Kowalski, M.L., et al.,*Classification and practical approach to the diagnosis and management of hypersensitivity to nonsteroidal anti-inflammatory drugs.*Allergy, 2013. **68** (10): p. 1219-32.

4. Dona, I., et al.,*Characteristics of subjects experiencing hypersensitivity to non-steroidal anti-inflammatory drugs: patterns of response.* Clin Exp Allergy, 2011. **41** (1): p. 86-95.

5. Zambonino, M.A., et al., *Drug provocation tests in the diagnosis of hypersensitivity reactions to non-steroidal anti-inflammatory drugs in children.* Pediatr Allergy Immunol, 2013. **24** (2): p. 151-9.

6. Quiralte, J., et al.,*Intolerance to nonsteroidal antiinflammatory drugs: results of controlled drug challenges in 98 patients.* J Allergy Clin Immunol, 1996. **98** (3): p. 678-85.

7. Stevenson, D.D., M. Sanchez-Borges, and A. Szczeklik, *Classification of allergic and pseudoallergic reactions to drugs that inhibit cyclooxygenase enzymes.* Ann Allergy Asthma Immunol, 2001. **87** (3): p. 177-80.

8. Dona, I., et al.,*NSAIDs-hypersensitivity often induces a blended reaction pattern involving multiple organs.* Sci Rep, 2018. **8** (1): p. 16710.

9. Aberer, W., et al., *Drug provocation testing in the diagnosis of drug hypersensitivity reactions: general considerations.* Allergy, 2003. **58** (9): p. 854-63.

10. Dona, I., et al., *Medical algorithm: Diagnosis and treatment of NSAIDs hypersensitivity.* Allergy, 2019.

11. Dona, I., et al., *Progress in understanding hypersensitivity reactions to nonsteroidal anti-inflammatory drugs.* Allergy, 2020. **75** (3): p. 561-575.

12. Kowalski, M.L., et al.,*Diagnosis and management of NSAID-Exacerbated Respiratory Disease (N-ERD)-a EAACI position paper.* Allergy, 2019. **74** (1): p. 28-39.

13. Ortega, N., et al.,*Practical guidelines for diagnosing hypersensitivity reactions to nonsteroidal anti-inflammatory drugs.* J Investig Allergol Clin Immunol, 2014. **24** (5): p. 308-23.

14. Izquierdo-Dominguez, A., et al.,*Statement of the Spanish Society of Allergology and Clinical Immunology on Provocation Tests With Aspirin/Nonsteroidal Anti-inflammatory Drugs.* J Investig Allergol Clin Immunol, 2020.**30** (1): p. 1-13.

15. Bindu, S., S. Mazumder, and U. Bandyopadhyay, *Non-steroidal anti-inflammatory drugs (NSAIDs) and organ damage: a current perspective.* Biochem Pharmacol, 2020: p. 114147.

16. Conaghan, P.G., *A turbulent decade for NSAIDs: update on current concepts of classification, epidemiology, comparative efficacy, and toxicity.* Rheumatol Int, 2012.**32** (6): p. 1491-502.

17. https://www.aemps.gob.es/medicamentosUsoHumano/observatorio/docs/AINE.pdf?x18026.

18. Perez-Sanchez, N., et al.,*Evaluation of Subjects Experiencing Allergic Reactions to Non-Steroidal Anti-Inflammatory Drugs: Clinical Characteristics and Drugs Involved.* Front Pharmacol, 2020. **11** : p. 503.

19. Brockow, K., et al., *EAACI position paper on how to classify cutaneous manifestations of drug hypersensitivity.* Allergy, 2019. **74** (1): p. 14-27.

20. Brockow, K., et al.,*General considerations for skin test procedures in the diagnosis of drug hypersensitivity.* Allergy, 2002. **57** (1): p. 45-51.

21. Goday-Bujan, J.J., et al.,*Photoallergic contact dermatitis from dexketoprofen: study of 6 cases.* Contact Dermatitis, 2006. **55** (1): p. 59-61.

22. Tavares Almeida, F., et al.,*Generalized bullous fixed drug eruption caused by ibuprofen.*Contact Dermatitis, 2019. **80** (4): p. 238-239.

23. Campo, P., et al., *Mediator release after nasal aspirin provocation supports different phenotypes in subjects with hypersensitivity reactions to NSAIDs.* Allergy, 2013.**68** (8): p. 1001-7.

24. Nizankowska-Mogilnicka, E., et al., *EAACI/GA2LEN guideline: aspirin provocation tests for diagnosis of aspirin hypersensitivity.* Allergy, 2007. **62** (10): p. 1111-8.

25. Fosbol, E.L., et al., *The pattern of use of non-steroidal anti-inflammatory drugs (NSAIDs) from 1997 to 2005: a nationwide study on 4.6 million people.*Pharmacoepidemiol Drug Saf, 2008. **17** (8): p. 822-33.

26. Duong, M., et al., *Usage patterns of 'over-the-counter' vs. prescription-strength nonsteroidal anti-inflammatory drugs in France.* Br J Clin Pharmacol, 2014.**77** (5): p. 887-95.

27. Valkhoff, V.E., et al.,*Population-based analysis of non-steroidal anti-inflammatory drug use among children in four European countries in the SOS project: what size of data platforms and which study designs do we need to assess safety issues?* BMC Pediatr, 2013. **13** : p. 192.

28. Kidon, M.I., et al., *Early presentation with angioedema and urticaria in cross-reactive hypersensitivity to nonsteroidal antiinflammatory drugs among young, Asian, atopic children.* Pediatrics, 2005. **116** (5): p. e675-80.

29. Kidon, M.I., et al.,*Nonsteroidal anti-inflammatory drug hypersensitivity in preschool children.* Allergy Asthma Clin Immunol, 2007. **3** (4): p. 114-22.

30. Sanchez-Borges, M. and A. Capriles-Hulett, *Atopy is a risk factor for non-steroidal anti-inflammatory drug sensitivity.* Ann Allergy Asthma Immunol, 2000.**84** (1): p. 101-6.

31. Bagheri, H., et al.,*Photosensitivity to ketoprofen: mechanisms and pharmacoepidemiological data.* Drug Saf, 2000. **22** (5): p. 339-49.

Figure 1

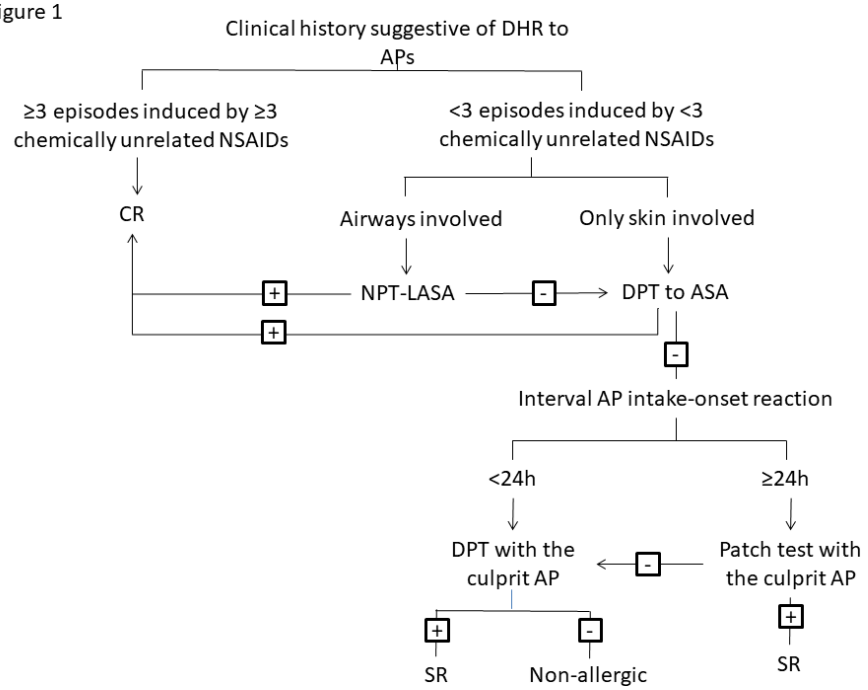

Figure 2