

How Can We Better Classify NSAID Hypersensitivity Reactions? – Validation from a Large Database

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Key Words

Nonsteroidal anti-inflammatory drugs • Classification • Drug hypersensitivity • Drug allergy • Drug provocation test

Abstract

Background: Hypersensitivity to nonsteroidal anti-inflammatory drugs (NSAIDs) is one of the most common drug hypersensitivities. Several clinical subtypes have been distinguished depending on symptomatology (respiratory, cutaneous, anaphylaxis), timing (immediate, delayed), underlying chronic disease (asthma, chronic urticaria) or putative mechanism of the reaction (allergic, nonallergic mediated). The aim of the present study was to better classify the many hypersensitivity reactions to NSAIDs. **Methods:** In the present retrospective study, during an 11-year study period, we collected data from all patients with a proven NSAID hypersensitivity. Reactions were classified according to clinical patterns, chronology, underlying diseases and the results of oral provocation tests into 5 and 7 groups in line with two published classifications, respectively. **Results:** Forty-nine and 88 out of 307 reactions (in 122 patients) could not be classified on the basis of the two previously published classifications. We created a new classification which could include all patient reactions. **Conclusions:** Our new classification is more suitable for clinical expression of NSAID hypersensitivity. It allows clinicians to identify patients at a high risk, based

on the clinical history and clinical manifestations. Moreover, it is helpful for a better understanding and teaching of these reactions.

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Introduction

Nonsteroidal anti-inflammatory drugs (NSAIDs) are among the most commonly used medications. They represent a very large class of widely prescribed drugs comprising more than 30 different compounds from several different chemically unrelated subclasses [1]. NSAIDs have anti-inflammatory, antipyretic and analgesic properties. The basic mechanism of their action is based on the inhibition of the enzyme cascade in the metabolism of arachidonic acid – cyclooxygenase 1 (COX-1) and cyclooxygenase 2 (COX-2) enzymes – resulting in an inhibition of prostaglandin production. The main side effects related to the use of NSAIDs include gastrointestinal and renal complications [2]. These are a result of the anti-inflammatory mechanism itself, and they seem to increase proportionally with the dosage. Among other side effects, hypersensitivity reactions may involve immunologic and nonimmunologic mechanisms. An adverse drug reaction is a noxious or unintended reaction to a drug that is administered in standard doses by the proper route for the

purpose of prophylaxis, diagnosis or treatment [3]. Allergic hypersensitivity comprises anaphylaxis, various cutaneous reactions and photosensitivity. NSAIDs can also be associated with nonallergic hypersensitivity related to disequilibrium in the arachidonic acid degradation pathways, even though the exact reasons by which this happens have not been well clarified [4]. This adverse event may be related to a prostaglandin E2 deficit, to an excess of cysteinyl leukotrienes and to some genetic polymorphisms [5]. Nonallergic hypersensitivity reactions may express themselves in the same way as allergic reactions, so that, clinically, it is not possible to distinguish between them. Patients who have adverse reactions to NSAIDs have very limited analgesic and anti-inflammatory therapeutic options, with difficulties finding pain relievers in daily life in general and in perioperative settings. The clinical presentation of NSAID-induced hypersensitivity reactions is not NSAID specific. It is heterogeneous, comprising several forms.

Although a typical clinical presentation of aspirin or other NSAID hypersensitivity may easily raise the suspicion of hypersensitivity to this class of drugs, oral challenge is often the ultimate means of firm diagnosis [6], while skin tests and *in vitro* tests are not currently recommended as a routine practice, with the exception of suspected IgE-mediated reactions (noncross-reactive) [7]. Drug provocation test indications, contraindications and security environment conditions have been carefully analyzed and published by the European Network for Drug Allergy (ENDA), the EAACI drug allergy interest group [8]. Considered to be the gold standard, we aimed to classify NSAID hypersensitivities according to the clinical patterns and the results of oral provocation tests. Using the Drug Allergy and Hypersensitivity Database [9], the objective of the present paper was to demonstrate whether or not patterns are well defined with little or no overlap [10]. The purpose of finding a new classification was to have the possibility of identifying patients at a high risk and with a rather high probability, based on clinical history and clinical manifestations, and therefore to identify patients before a potentially dangerous reexposure. Moreover, a clear classification would greatly facilitate the teaching and management of such reactions.

Materials and Methods

Patients

All consecutive patients who presented with a compatible past clinical history of hypersensitivity reaction to NSAIDs were included in the present study. They were referred to the Allergy De-

partment of the University Hospital of Montpellier, France, between January 1998 and December 2008. The drug allergy workup proved that their reaction was indeed due to NSAIDs by means of a drug provocation test. Eighteen different NSAIDs were tested, belonging to all different chemical subgroups, with the exception of pyrazolones (aspirin, carbasalate calcium, celecoxib, diclofenac, glycol salicylate, ibuprofen, ketoprofen, mefenamic acid, meloxicam, naproxen, niflumic acid, nimesulide, noramidopirin, paracetamol, fenoprofen, piroxicam, tenoxicam, tiaprofenic acid). Manifestations included rhinitis, conjunctivitis, bronchospasm, cutaneous exanthemas including urticaria and maculopapular eruptions, angioedema and anaphylaxis. We recorded all the manifestations presented by the patients, and in a single patient, a combination of symptoms was possible as well. We considered anaphylaxis as a rapid reaction suggesting allergy and affecting at least 2 different organs (for example, urticaria and bronchospasm) with or without hypotension. Hypotension was defined as a decrease of 30% or as a 30 mm Hg lowering of systolic blood pressure when compared to normal values as described elsewhere [6, 11].

Patients presenting with a suspicion of an isolated allergy to paracetamol/acetaminophen were excluded since this drug was not considered as an NSAID at the beginning of the survey [12]. Patients who had experienced severe life-threatening skin reactions (vasculitis, toxic epidermal necrolysis and Steven Johnson syndrome), drug-induced autoimmune diseases or severe organ involvements (such as cytopenias, hepatitis, drug reaction with eosinophilia and systemic symptoms – DRESS) were not included in the study either since these reactions contraindicate the provocation test. Forced expiratory volume in 1 second values were at least 80% of the predicted value in patients who had presented a bronchospasm during the hypersensitivity episode. Asthmatic patients were excluded from the study if they presented a high probability of a so-called aspirin-exacerbated respiratory disease, since aspirin-induced asthma is a clearly defined clinical entity with a strong positive predictive value of the clinical history [13], which lowers the utility of oral provocation in daily practice (the key tool of our drug allergy workup in this study). Patients had not been taking any H1-antihistamines or any drugs that could have affected the drug provocation. Patients with a rapid-onset reaction and those on β -blockers were asked to visit their cardiologist/ophthalmologist/general practitioner in order to stop the drug 2 days prior to the test.

Drug Allergy Workup

Clinical data were registered using the ENDA drug allergy questionnaire [14]. Drug provocation tests, using the drug suspected to cause the reaction, were performed under strict hospital surveillance as previously described [6] and at least 4 weeks after the last reaction in all patients. Patients had to ingest increasing doses of the drug every 30 min until the usual daily dose was administered or until any hypersensitivity symptom occurred. Administration was single-blinded and performed on the ward by a physician with full resuscitation back up. Single doses were especially prepared by the hospital pharmacy unit. Patients with a history of anaphylactic shock had intravenous catheters in place during the entire test. The final provocation dose in case of a negative provocation test was the defined daily dose of the respective NSAIDs.

Challenge response was considered as positive whenever at least one of the following criteria was fulfilled [6]: urticaria, angioedema, macular and/or papular lesions in any localization, a

Table 1. Characteristics of the included patients, according to the Quiralte et al. [10] classification – 49 reactions (in 22 patients) could not be classified

NSAID reactivity patterns	Clinical form	Associated underlying disease	Reactions, n	Patients n
Cross-reactive syndromes	<i>Type 1:</i> Nasoocular and/or asthmatic reaction	Rhinitis and/or bronchial asthma with or without nasosinusal polyposis	22	8
	<i>Type 2:</i> Urticaria and/or angioedema	Chronic urticaria/angioedema	102	38
	<i>Type 3:</i> Isolated periorbital angioedema	Atopic disease (rhinitis and/or bronchial asthma and NSAID-sensitive mite ingestion reaction syndrome)	26	9
Selective syndromes	<i>Type 4:</i> Systemic anaphylaxis and urticaria	None	2	1
Miscellaneous syndromes	<i>Overlap reaction:</i> Selective reaction (oral allergy syndrome-like, urticaria and asthma) in patients with atopic disease (rhinitis and/or bronchial asthma)		90	4
	<i>Nonurticarial reaction:</i> Cross-reactive macular and/or papular exanthemas		4	2
	<i>Systemic reaction:</i> Cross-reactive anaphylaxis-like reaction in some cases of type 1 and type 2 patients during challenge with potent COX-1/COX-2 inhibitors		12	5

decline of more than 20% in FEV1, sneezing, rhinorrhea, nasal blockage, conjunctivitis, anaphylaxis. If the result of the test was positive, we searched for an alternative NSAID by drug provocation, at least 4 weeks later, utilizing an NSAID belonging to a different chemical class. All data were collected in the Drug Allergy and Hypersensitivity Database (DAHD®) using FileMaker Pro 7 software. Categorical data were expressed in frequencies and percent, continuous data in means and standard deviations. Analysis was conducted under SAS v9.2 (SAS Institute, Cary, N.C., USA).

Classification of the NSAID Hypersensitivity Reactions

Cases were classified according to the clinical patterns of the initial reactions and those of the oral provocation tests (respiratory, cutaneous, anaphylaxis), whether or not one or multiple NSAID classes were involved, the timing (occurring less or more than 24 h after the last drug intake), possible underlying chronic disease (asthma, chronic urticaria, chronic rhinosinusitis, atopy as defined by the presence of at least one positive skin-prick test to the common aeroallergens of the Montpellier area) or putative mechanism of the reaction (allergic, nonallergic mediated) [15].

We first used the classification published by Quiralte et al. [10] (table 1). Since it was not suitable for all of our patients, we also utilized the newly created ENDA classification (table 2) [7], and because some cases were still left behind, we developed our own new classification (table 3).

Results

Patient Characteristics

During the study period (January 1998 to December 2008), 1,178 drug provocation tests with NSAIDs were performed on 980 patients (64.7% female, mean age 38.4 ± 18.6 years). Dropouts were only those patients who did not come back to continue their allergy workup.

122 patients (60.9% female, mean age 36.5 ± 17.5 years) presented positive results (12.5%), with an overall total of 307 reactions (mean number of reactions per patient: 2.6 ± 1.1), 105 negative challenges for finding an alternative drug and 3 inductions of tolerance. Three other patients could not be included. The first of these did not undergo the first provocation test. He presented with nasal polyposis and asthma and reported a reaction of urticaria induced by paracetamol and aspirin. Tolerance induction to aspirin was indicated to quickly find a safe treatment. He probably suffered from a Widal syndrome. The second patient, who had a history of anaphylaxis to ibuprofen, presented a reaction characterized by isolated urticaria during the drug provocation with ibuprofen and refused further tests. The original reaction reported by the patient was actually associated with some physical exercise, which may have worsened the severity of the initial clinical manifestation. The third patient with one episode of NSAID-induced rhinoconjunctivitis, which was demonstrated by a first drug provocation test, found an alternative safe drug right after their second challenge. Therefore, their condition could not be classified as ‘cross-reactive syndrome’ or as ‘multiple NSAIDs induced’ or a ‘single drug induced with this clinical manifestation’.

In our cohort of 122 patients, 105 were adults (mean age 40.4 ± 14.2 years) and 17 were children (mean age 10.7 ± 4.1 years). The time between initial reaction and drug allergy workup was 46.4 ± 87.7 months. When considering children only, this time was 70.3 ± 135.8 months.

Table 2. Characteristics of the included patients, according to the ENDA classification [7] – 88 reactions (in 33 patients) could not be classified

Time of reaction	Clinical manifestation	Type of reaction	Underlying disease	Putative mechanism	Reactions, n	Patients n
Acute ¹	Rhinitis/asthma	Cross-reactive	Asthma/rhinosinusitis	COX-1 inhibition	17	7
	Urticaria/angioedema	Cross-reactive	Chronic urticaria	COX-1 inhibition	66	24
	Urticaria/angioedema	Multiple NSAIDs induced	None	Unknown, presumably related to COX-1 inhibition	94	34
	Urticaria/angioedema/anaphylaxis	Single drug induced	Atopy Food allergy Drug allergy	IgE mediated	38	22
Delayed ²	Fixed drug eruptions	Single drug induced or multiple drug induced	Usually none	T cell mediated (type IV)	4	2
	Severe bullous skin reaction			Cytotoxic T cells		
	Maculopapular drug eruptions			NK cells		
	Pneumonitis			Other		
	Aseptic meningitis					
	Nephritis					
	Contact and photocontact dermatitis					

¹ Reaction occurs immediately or up to 24 h after drug exposure. ² Reaction occurs more than 24 h after exposure.

Table 3. Characteristics of the included patients, according to our new classification – all reactions could be classified

Time of reaction	Clinical manifestation	Type of reaction	Underlying disease	Putative mechanism	Reactions, n	Patients n
Immediate ¹	Rhinitis-asthma and/or urticaria-angioedema	Cross-reactive	Asthma/rhinosinusitis and/or chronic urticaria	COX-1 inhibition	136	50
	Urticaria-angioedema and/or rhinoconjunctivitis	Multiple NSAIDs induced	No underlying chronic disease or atopy or rhinoconjunctivitis	Unknown, presumably related to COX-1 inhibition	123	46
	Urticaria-angioedema/anaphylaxis	Single drug induced	Atopy or food allergy or drug allergy	IgE mediated	42	22
Non-immediate ²	Fixed drug eruptions	Single drug induced or multiple drug induced	Usually none	T cell mediated (type IV)	4	2
	Severe bullous skin reaction			Cytotoxic T cells	2	2
	Maculopapular drug eruptions			NK cells		
	Angioedema			Other		
	Pneumonitis					
	Aseptic meningitis					
	Nephritis					
	Contact and photocontact dermatitis					

¹ Reaction occurs immediately or up to 6 h after drug exposure. ² Reaction occurs more than 6 h after exposure.

Table 4. Number of patients with different underlying diseases

Underlying diseases	Patients affected
Chronic urticaria	23
Asthma	17
Chronic rhinosinusitis	2
Chronic urticaria and asthma	5
Chronic urticaria and rhinosinusitis	2
Chronic urticaria, rhinosinusitis and asthma	1

NSAIDs Involved

The NSAIDs involved in the referred reactions were aspirin (38.76%), ibuprofen (15%), diclofenac (2.28%), paracetamol (4.23%, whether or not associated to dextropropoxyphene), ketoprofen (8.8%), naproxen (1.95%), tiaprofenic acid (6.19%), niflumic acid (6.89%), tenoxicam (1.3%), piroxicam (11.4%), carbasalate calcium (0.32%), nimesulide (0.97%), celecoxib (2.28%), noramidopirin (0.32%), mefenamic acid (0.32%), glycol salicylate (0.32%), meloxicam (0.32%) and fenoprofen (0.32%).

Underlying Diseases

Whether or not an underlying disease was present is crucial in the classification of these reactions. Twenty-three patients (24.1%, compared to 17.7% of the patients with negative results, $p = 0.15$) were affected by clinically controlled asthma (they were not excluded from the study since the NSAID reaction they first experienced did not include any respiratory symptom). All the asthmatic patients presented a clinically controlled asthma caused by an atopic sensitization while none presented an asthma related to an aspirin-exacerbated disease. Thirty patients presented chronic urticaria/angioedema. Some patients presented different chronic diseases, as detailed in table 4. Eighty-eight were atopic (72.1%, compared to 55.3% of the patients with negative results, $p < 0.01$), and 3 suffered from nasal polyposis (one of them was asthmatic). Forty-three (48.9%) of the atopic patients were sensitized to house dust mites.

Clinical Reactions

Amongst the 307 reactions, we were able to document 126 episodes of urticaria associated to angioedema with underlying disease like chronic urticaria or asthma (in 45 patients), 31 episodes of urticaria with or without angioedema, without associated underlying disease (in 12 patients), 94 episodes of urticaria associated with atopic diseases (in 40 patients), 26 episodes of isolated periorbital

angioedema (in 10 patients), 17 episodes of rhino-conjunctivitis and/or bronchospasm (in 7 patients), 4 episodes of nonurticarial (maculopapular) skin eruptions (in 2 patients), 5 episodes of systemic reaction such as anaphylaxis without a drop in blood pressure (in 3 patients), 2 episodes of anaphylactic shock (in 1 patient) and 2 episodes of nonimmediate angioedema without underlying disease (in 2 patients). Fifty-one out of 122 patients suffered from chronic underlying diseases, such as chronic urticaria/angioedema (23 patients), asthma (17 patients), chronic rhinosinusitis with or without nasal polyposis (2 patients), chronic urticaria/angioedema associated with asthma (5 patients), urticaria/angioedema associated with chronic rhinosinusitis with or without nasal polyposis (2 patients), urticaria/angioedema associated with asthma and chronic rhinosinusitis with or without nasal polyposis (1 patient), and nasal polyposis (1 patient; online suppl. table 1; for all online suppl. material, see www.karger.com/doi/10.1159/000337660).

Single versus Multiple Reactions

It was also crucial to document the presence of multiple reactions. This information came from both the clinical history and the results of the drug provocation tests. We found 39 patients who reacted to a single drug. We were not able to find a safe NSAID alternative drug for 30 patients: 16 patients did not want to continue the testing after a first positive challenge and 14 patients did not want to search for a safe NSAID after more than two positive challenges. We did find an alternative for the remaining 89 subjects enrolled in the study: a selective anti-COX-2 for 29 patients, one anti-COX-1 for 60 patients (for 8 patients one anti-COX-1 and one anti-COX-2) and 3 patients urgently needing an NSAID underwent tolerance induction (1 to aspirin, 1 to diclofenac and 1 to celecoxib).

Classification of the NSAID Hypersensitive Reactions

We were unable to classify the 3 patients who underwent tolerance induction. We then tried to classify the other patients according to the classification of Quiralte et al. [10] (table 1). This classification was not suitable for all of the patients. Indeed, 49 reactions (in 22 patients) did not fit such a classification: 45 reactions (in 19 patients) of urticaria were not associated with any of the above underlying diseases, 2 reactions of urticaria in 1 patient without anaphylaxis and without underlying diseases and 2 delayed angioedema (in 2 patients). The newly created ENDA classification (table 2) [7] was not suitable for all of our patients either, since 88 reactions (in 33 patients) did not fit perfectly into a group: 32 urticaria reactions

(in 12 patients) were not associated with 'chronic urticaria/angioedema' but were associated either with asthma, chronic rhinosinusitis or to nasal polyposis; 31 urticaria reactions (in 11 patients) induced by multiple NSAIDs were detected in patients simply presenting with atopy or rhinoconjunctivitis and without any underlying chronic disease; 2 reactions of urticaria and asthma in 1 patient with chronic asthma and urticaria could not be classified either; 11 reactions of angioedema or urticaria and asthma in 3 patients with chronic urticaria and asthma or rhinosinusitis; 10 reactions of urticaria and asthma in 4 patients with chronic asthma, and 2 reactions of delayed angioedema (in 2 patients).

Finally, based on these results, we created a new classification (table 3). Using our new table, we were actually able to classify all 122 patients; we added the new clinical manifestation of 'nonimmediate angioedema' that appeared between 6 and 24 h after the challenge.

Discussion

NSAID hypersensitivity is common in clinical allergy practice and a drug provocation test is often needed to identify an alternative safe drug for the patient [16]. Reactions may occur from a few minutes up to 24 h after NSAID ingestion, but they generally develop within a few hours. Hypersensitivity reactions caused by a single NSAID, with tolerance to other NSAIDs, argue against a pharmacokinetic imbalance as the driving mechanism [17]. The exact pathophysiology of these reactions is as yet unknown: a nonallergic hypersensitivity, an IgE-dependent allergic reaction or a type IV allergic reaction may be the underlying mechanism leading to the clinical manifestation. When a patient is declared as allergic to a certain NSAID (or to more than one molecule), he/she needs to always carry an allergy card stating all suspected and proven allergies and safe alternatives (and/or have this information in his/her electronic files), so that health care providers are informed of the problem.

Patients with NSAID hypersensitivity often present an associated underlying chronic disease such as asthma, chronic urticaria or rhinosinusitis, which could complicate both the clinical manifestations of the reaction and the safety of the challenge. In our study, we excluded those patients who, taking into consideration their history, were most likely to react severely to the suspected drug during the challenge, including NSAID-exacerbated asthmatics. This background was taken into account in the different attempts to classify the many clinical presentations of

NSAID hypersensitivity. Indeed, in the literature, we found several different criteria for a clinical classification of the reactions induced by NSAIDs. Stevenson et al. [18] and Gollapudi et al. [19] followed by Quiralte et al. [10, 20] first proposed a classification according to 3 main criteria. The originality of the Stevenson et al. [18] classification is that it gives insight into the management. It is mostly based on the clinical history and not on drug provocations. According to this classification, clinical histories can be classified into four patterns: respiratory, cutaneous, mixed and systemic. The Quiralte et al. [10] classification of NSAID-induced hypersensitivity reactions is based on drug provocation and separates 7 different groups of reactors, each with well-defined clinical characteristics. Skin testing and in vitro testing may be useful mainly in IgE-dependent reactions, although this is not sufficiently validated [21, 22]. Drug provocations not only rule out the diagnosis in some cases, they enable classification and also find a safe alternative NSAID. In the present study, not all our patients could fit into this classification. We thus proposed to classify patients by taking into consideration the most severe clinical manifestation they had experienced (table 3). The reactions were then classified into immediate and nonimmediate, depending on whether they occurred within or later than 6 h after the drug exposure.

As for immediate reactions, for those patients reporting an episode of asthma or rhinitis, associated or not with chronic urticaria/angioedema, we consider the reaction to be due to COX-1 inhibition, and highly likely to cross-react with other anti-COX-1 drugs. The asthmatic patients with a clear NSAID trigger that we excluded from this study belong to this group. The same clinical forms can be seen without any underlying diseases, in which case we cannot exclude that the reaction is due to a COX-1 inhibition, but we expect the reaction to be triggered by other molecules as well. Finally, as for those immediate reactions in which the major event includes an episode of urticaria, angioedema or anaphylaxis, the reaction can be considered to be IgE mediated and associated with the single culprit molecule. These patients are atopic, or have a history of food allergy or other drug allergies. Nonimmediate reactions, including fixed drug eruptions, severe bullous skin reaction, maculopapular drug eruptions, delayed angioedema, pneumonia, aseptic meningitis, nephritis or contact dermatitis, are mediated by T cells, cytotoxic T cells, NK or other cells. These patients react to a single molecule and show no underlying diseases. These reactions do exist, although they are much less frequent; however, most of them could not be included in our study, which was based on provocation tests.

Our new classification demonstrates two important advantages regarding NSAID hypersensitivity reactions: one is related to communication and the other to clinical practice. The real advantage of the present classification is that, first of all, it allowed us to properly include in the chart all the patients we investigated in our unit. Moreover, as we already use such a classification in our daily practice, it has become much easier to decide which steps need to be followed to choose the drug to be tested (same drug, alternative drug from another NSAID family, or a COX-2 inhibitor directly). Thus, when a patient reports a history of exacerbated chronic urticaria or asthma after NSAID ingestion, clinicians would directly suggest a COX-2 inhibitor as a safe alternative. However, it is possible in some cases that the first episode of NSAID-in-

duced urticaria may be followed some years later by chronic urticaria [23]. Such an event may be considered to be similar to the onset of asthma induced by aspirin. Unlike the ENDA classification, we grouped all chronic underlying diseases in our table, pointing out a possible common pathophysiological mechanism that could trigger the hypersensitive reaction after contact with NSAIDs. Our new chart makes it easier to explain to both patients and students the many hypersensitivity reactions to NSAIDs, simplifying the mechanisms and relating them to the clinical manifestations. Finally, another major clinical innovation of this classification is the highlighting of nonimmediate angioedema as a form of nonimmediate reaction to NSAIDs, which was not included in the previous classifications.

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Online Supplementary Table S1 – Clinical reactions in 122 patients

Symptoms	Underlying disease	Drugs to which the patients reacted					
Urticaria	Chronic urticaria and/or asthma	asp	ibu				
		asp	par	asp	ket		
		asp	asp	nap			
		asp	pir	nif	pir		
		asp	ibu				
		asp					
		ten	ten				
		nap	asp				
		mel	phe	pir	dic	ten	ibu
		pir	tia	asp			
		ibu	asp	asp			
		ket	asp				
		asp	tia	nif			
		asp	asp				
		asp	asp				
		asp	ibu	ten	par	nim	
		ibu	nap	asp	pir		
		asp	tia	nif	nor		
		asp	ket	pir			
		asp	ibu	asp			
		ibu	nap	asp	kete	par	
		asp	pir	dic	ibu	asp	
		asp	tia	par	pir		
		ibu					
		asp	asp				
		asp	pir	asp			
		nif	nif				
		asp	asp				
		ket					
		ibu					
		dic	asp	nif			
		asp	ibu	pir			
		tia					
		ket	ibu	asp			
		asp	pir	nim	cel	par	
		ibu	asp	ket	cel		
		asp	cel				
		tia	ket	pir			
		asp	pir				
		asp	par	asp			
		ket	nim				
		nap	gly	ibu	pir	mef	
		asp					
		ibu					
		asp	ket				
Urticaria	None	dic	pir				

Urticaria	Atopy	asp	ket				
		asp	pir	nim			
		pir	asp	par	ibu		
		asp	ibu				
		asp	asp				
		ibu	asp	asp	tia		
		asp	ket				
		ket	ibu	asp			
		asp	ket				
		asp	pir	ket			
		ibu	nif				
		ket	asp	nif			
		asp	asp				
		ibu	ket	pir	asp		
		asp	pir				
		cel	cel				
		asp	tia				
		pir	pir				
		par	ibu	asp			
		asp	ibu	pir			
		ibu	ibu				
		asp	asp				
		asp	ibu				
		asp	ibu	pir			
		asp					
		ibu	ibu				
		ket	ibu				
		asp	ibu	asp			
		asp	asp				
		asp	asp				
		asp	ket	ibu			
		asp	pir	ket	par	tia	
		asp	pir				
		asp	tia	dic	pir		
		ibu	asp	ibu			
		asp					
		asp	pir				
		asp	nif	dic	pir	tia	
		asp					
		asp	ibu				
		ket	pir				
		ibu	tia				
		asp	nap				
		ibu	car	par			
		asp	ket				
		tia	tia				
		ibu	asp	ibu			
		ket	asp				
		ket					
		ibu	ibu				

Angioedema isolated	None	asp					
		asp	asp				
		pir	tia	asp			
		asp	nif	tia			
		asp	nif	ket			
		asp	ibu	asp			
		tia	asp				
		pir	asp	ibu	par		
		asp	ket				
		asp	asp				
Asthma	Chronic urticaria and/or asthma and/or polyposis	asp	pir				
		asp	asp				
		tia	asp				
		asp	ibu				
		asp	asp				
		asp	ket				
		dic	ibu	nif	par	asp	
		asp	par				
Anaphylaxis without shock	None	asp	asp				
		cel	cel				
		nif					
Macular papular reaction	None	pir					
		nif	tia	asp			
Anaphylactic shock	None	asp	asp				
Non immediate angioedema	None	asp					
		pir					

asp: aspirin; car: carbasalate calcium; cel: celocoxib; dic: diclofenac; gly: glycol salicylate; ibu: ibuprofen; ket: ketoprofen; mef: mefenamic acid; mel: meloxicam; nap: naproxen; nif: niflumic acid; nim: nimesulide; nor: noramidopirin; par: paracetamol; phe: phenoprofen; pir: piroxicam; ten: tenoxicam; tia: tiaprofenic acid.