

Challenge-Based Clinical Patterns of 223 Spanish Patients With Nonsteroidal Anti-Inflammatory-Drug-Induced-Reactions

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■ Abstract

Background: The single-blind, placebo controlled oral challenge (SBPCOC) is the definitive way to diagnosis nonsteroidal anti-inflammatory drug (NSAID)-induced reactions.

Objective: To evaluate 223 NSAID-sensitive patients by means of SBPCOC, and to describe the main clinical patterns found.

Methods: A prospective study was carried out, including 2 patient groups with case histories consistent with NSAID-induced reactions. Of the 223 patients, 174 were diagnosed on the basis of a positive SBPCOC. The second group consisted of 49 patients who were referred because of a documented history of anaphylaxis after taking NSAIDs, and these underwent SBPCOC with potent cyclooxygenase (COX)-1/COX-2 inhibitors, except those reported as being responsible for the reaction. The type of SBPCOC reaction, the NSAID reactivity pattern, and the associated diseases were the main classification criteria.

Results: Two broad categories of NSAID-induced reactions were identified: the cross-reactive and selective syndromes. The 150 patients who showed cross-reactive syndromes included 3 types of diseases: type 1, patients with rhinitis and/or asthma who developed nasoocular and/or asthmatic reactions (n=40); type 2, patients with or without chronic urticaria who presented urticaria/angioedema (n=59); and type 3, atopic patients with isolated periorbital angioedema (n=51). In contrast, the selective syndromes, or type 4, included 50 patients who developed anaphylaxis, as well as 11 patients with urticaria during SBPCOC. Finally, a miscellaneous group of reactions not matching any of the above types was identified (n=12).

Conclusions: NSAID-sensitive patients can be classified into 4 different groups of reactors, each with well-defined clinical characteristics. Thus, a clinical classification of this NSAID-induced reaction complex is proposed.

Key Words: NSAID sensitivity. Asthma. Nasoocular reaction. Angioedema. Urticaria. Anaphylaxis. Classification.

■ Resumen

Antecedentes: La provocación oral simple-ciego, controlada con placebo (POS CCP) es el método de elección para el diagnóstico de las reacciones idiosincrásicas inducidas por fármacos antiinflamatorios no esteroideos (AINE).

Objetivos: Describir y clasificar, a través de la POS CCP, una población de pacientes con reacciones a AINE.

Métodos: Se incluyeron 223 pacientes con reacciones a AINEs en un protocolo de POS CCP previamente diseñado. Ciento setenta y cuatro mostraron una POS CCP positiva. Los 49 restantes exhibieron una reacción anafilactoide, que contraindicó el uso del AINE implicado durante la POS CCP. Se clasificaron según 3 criterios: el tipo de reacción durante la POS CCP, el patrón de reactividad entre AINEs y la enfermedad concomitante asociada.

Resultados: Se identificaron 150 pacientes que presentaron síndromes asociados con reactividad múltiple entre AINE durante la POS CCP y que fueron incluidos en 3 tipos: i) tipo 1, pacientes con rinitis y/o asma que desarrollaron una reacción nasoocular y/o asmática (n=40); ii) tipo 2, pacientes con o sin urticaria/angioedema crónicos que presentaron urticaria/angioedema (n=59); y iii) pacientes atópicos con angioedema periorbitario aislado (n=51). Sesenta y un pacientes mostraron un patrón selectivo frente a un AINE específico y fueron clasificados como tipo 4. Este grupo estaba constituido por 50 pacientes con anafilaxia, y 11 pacientes que mostraron urticaria durante la POS CCP. Los

restantes 12 pacientes presentaron un grupo diverso de reacciones que no pudieron incluirse en ninguno de los tipos anteriores.
Conclusiones: Las reacciones a AINE son un conjunto heterogéneo de síndromes, con unas características clínicas muy definidas. Se propone una clasificación clínica de estas reacciones.

Palabras Clave: Reacciones a AINE. Asma. Reacción nasooocular. Angioedema. Urticaria. Anafilaxia. Clasificación.

Introduction

Controlled oral challenge is the only definitive way to diagnose the reactions caused by nonsteroidal antiinflammatory drugs (NSAIDs) [1]. These challenge-proven responses are a wide group of disorders that includes respiratory [2], cutaneous and anaphylactoid reactions [1,3,4], the so-called NSAID-induced reaction complex (NRC) [5].

The mechanisms of NRC are unknown, but two general hypotheses have been proposed. The first postulates enzymatic activity inhibition of at least the cyclooxygenase (COX)-1 isoform that may inhibit prostaglandin synthesis [6] and thus dysregulate the 5-lipoxygenase pathway, with cys-leukotriene hyperproduction in some susceptible patients [7]. All NSAIDs that inhibit the COX-1 isoform could precipitate the reaction [6]. For this reason, cross-reactivity among COX-1 inhibitor NSAIDs can be demonstrated in all patients with respiratory reactions [2] and in most patients with cutaneous reactions (multiple reactors) [1]. The second mechanism is applicable to only a small subset of patients with NRC, namely those with systemic anaphylaxis [1,4,5]. Recently, Himly et al [8] have demonstrated an immunoglobulin (Ig) E-mediated response against propyfenazone in patients with anaphylaxis caused by this NSAID. We have previously demonstrated that most patients with NSAID-induced systemic anaphylaxis can react only to one specific NSAID and that they tolerate other COX-1 inhibitor NSAIDs in a controlled oral challenge (selective reactors) [1,3-5].

At least, two subsets of these patients with NRC may have an associated underlying disease. In fact, around 10% of patients with moderate-to-severe asthma and 30% of those with chronic urticaria/angioedema may present a nasooocular/asthmatic [2] or urticarial [9] reaction after NSAID exposure at some time in their lives.

Based solely on these facts, in 1996 we proposed the 3 main criteria for a clinical classification of NRC: the clinical syndrome that occurred during controlled oral challenge, the pattern of reactivity among NSAIDs and the existence of other underlying diseases [1]. Those criteria were also used in the classification proposed by Stevenson et al [10] in 2001, in which the main NRC groups were exclusively established on the basis of the clinical records of 5 patients, and no challenges were performed in order to confirm these reactions. Recently, Sanchez-Borges et al [11] have reviewed the clinical features and the management of Stevenson's clinical patterns of reactions: the respiratory, cutaneous, systemic and mixed (or blended).

However, evidence suggests that some patients described in the literature as having these well defined NRC patterns may have certain clinical characteristics that distinguish them as a distinct entity. For example, we have previously characterized

an unusual skin manifestation of NRC in atopic patients, known as isolated periorbital angioedema [1,12].

In this article we evaluated the clinical features of single-blind, placebo controlled oral challenge (SBPCOC) carried out in 223 Spanish patients with NRC, the patterns of reactivity among NSAIDs, and the existence of associated underlying diseases. Our findings support a new working classification of these NSAID-induced reactions.

Patients and Methods

Patient Selection

Two groups of NSAID-sensitive patients were recruited for the study. The first group consisted of 174 patients with positive response during SBPCOC with NSAIDs. Patients reported a previous history of NSAID intolerance. Episodes included rhinitis, bronchial asthma, mucosal and/or dermal edema, and cutaneous exanthems of any type. The second group consisted of 49 patients who exhibited clinical evidence of anaphylaxis after NSAID intake on admission to the Emergency Room (ER) of our hospitals. Based on clinical records from ER, anaphylaxis was defined as the presence of urticaria and/or angioedema plus hypotension (systolic blood pressure below 90 mmHg) and/or laryngeal edema. The following clinical data were collected: age, sex, associated underlying disease if any, and clinical characteristics of the history of adverse reactions (ie NSAIDs involved, dose, time elapsed between administration of the NSAIDs and the beginning of the reaction, and symptoms experienced).

Subjects were diagnosed as being atopic if they showed rhinitis and/or bronchial asthma, with a positive skin prick test (a wheal of 3 mm greater than the negative control) and specific IgE values >0.7 kU/L, as measured by the ImmunoCAP System (Pharmacia Diagnostics, Uppsala, Sweden) to one or more of the following allergens: *Lolium perenne*, *Olea europaea*, *Cupressus arizonica*, *Platanus acerifolia*, *Artemisia vulgaris*, *Salsola kali*, *Parietaria judaica*, *Plantago lanceolata*, *Dermatophagoides pteronyssinus*, *Lepidoglyphus destructor*, *Tyrophagus putrescentiae*, *Alternaria alternata*, *Cladosporium herbarum*, *Aspergillus fumigatus*, dog and cat danders (Bial-Aristegui, Bilbao, Spain).

None of the patients had episodes of urticaria or angioedema in the week before challenge, and forced expiratory volume in 1 second (FEV₁) values were at least 80% of predicted, with an absolute value greater than 1.5 L. Drugs that could interfere with the results of SBPCOC, eg H₁ receptor antagonists, were discontinued 48 hours before challenge, except in those cases with chronic urticaria in which antihistamine therapy was

Table 1. Nonsteroidal Anti-Inflammatory Drugs and Doses Used for Single-Blind, Placebo Controlled Oral Challenge.*

Category	Drug	Doses
Placebo	Lactose	
Highly selective COX-2 inhibitor	Celecoxib	50, 100, 200 †
Preferential COX-2 inhibitor	Meloxicam	7.5, 15 mg †
Weak, nondiscriminatory COX-1/COX-2 inhibitor	Paracetamol	100, 250, 500, 1000 mg †
Potent, nondiscriminatory COX-1/COX-2 inhibitor	Piroxicam	10, 20 mg ‡
	Diclofenac	25, 50 mg ‡
	Ibuprofen	50, 150, 250, 600 mg †
	Dipyrrone	10, 50, 125, 250, 575 mg † ¶
	Acetylsalicylic acid	50, 100, 250, 500 mg § **

*Drugs were administered in opaque gelatin capsules at the following intervals between each dose: † 60 minutes, ‡ 120 minutes and § 180 minutes. || Three doses, ¶ four doses or ** two doses were administered on the first day, and ||, ¶ one dose or ** two other doses on the second day. COX indicates cyclooxygenase.

continued, if from the aspect of clinical management this was necessary, in order to avoid a false positive response. Written informed consent from the patients (or their parents, if they were younger than 18 years old) was obtained, and the protocol was approved by the Investigation and Ethics Committees of our Hospitals.

Controlled Oral Challenge

All patients were included in a previously published SBPCOC protocol [1,5]. The dosing protocol for the SBPCOC is summarized in Table 1. A detailed description of the challenge procedure has been described elsewhere [1,5]. Briefly, each SBPCOC was carried out separately, and at least 7 days were allowed to elapse after a positive challenge response. First, patients were challenged with a highly selective COX-2 inhibitor, celecoxib. Then, if no response occurred (ie, there was no evidence of reaction), successive SBPCOCs with the next drugs were performed, involving meloxicam (a NSAID that has been found to be a preferential COX-2 inhibitor), paracetamol (a weak non-discriminatory COX inhibitor), and at least one of the following potent, non-discriminatory COX-1/COX-2 inhibitors: piroxicam, diclofenac, dipyrrone, ibuprofen and acetylsalicylic acid. Each patient was challenged with the first drug (including placebo) not involved in a previous reaction. If no response occurred, successive challenges with the next drugs were performed. The number of SBPCOCs was individualized for each patient depending on clinical history and the NSAID involved in the previous reaction. When a previous reaction suggested anaphylaxis, we use neither the drug involved in the episode, nor the other structurally related NSAIDs in the SBPCOC [1,4,5].

The challenge response was considered positive if it fulfilled at least one of the following criteria [1,5]: 1) a decline of more than 20% in FEV₁; 2) sneezing rhinorrhea, nasal blockage, conjunctival injection and oropharyngeal itching; 3) pruritic and erythematous areas raised over normal skin; 4) macular and/or papular areas in any localization; 5) swelling of skin and/or external mucosa, and 5) systemic anaphylaxis: urticaria and/or angioedema plus hypotension (a 30 mmHg

decrease in systolic blood pressure) and/or laryngeal edema. The clinical characteristics of each SBPCOC (symptoms, NSAID involved, dose and time elapsed between the NSAID intake and the beginning of the reaction) were also recorded. During the challenge procedure, patients were clinically monitored at 15 minutes, 30 minutes and every hour after administering each NSAID or placebo dose, or at any time when other symptoms were reported by the patient.

Those patients who had a positive SBPCOC response with a NSAID which was not involved in a previous reaction or was not chemically related were included in the multiple reactivity pattern group. Otherwise, patients reacting exclusively with the NSAID involved in a previous reaction, and who tolerated at least one potent COX-1 inhibitor NSAID, were allocated to the selective reactivity pattern group.

Statistical Analysis

The χ^2 test was used for comparing the prevalence of atopy among the different groups of NSAID reactors. A *P* value of .05 or less was considered to indicate a significant difference.

Results

Patients

Two hundred twenty three patients (156 females and 67 males), whose ages ranged from 5 to 78 years (mean 32.2 years), were included in the study. The patients referred for evaluation had 317 documented episodes of NSAID reactions, distributed as follows: angioedema and urticaria, 94 episodes (29.7%); angioedema exclusively, 92 episodes (29.0%); anaphylaxis, 51 episodes (16.0%); urticaria and angioedema with nasoocular and/or asthmatic reaction, 48 episodes (15.1%); respiratory manifestations exclusively, 27 episodes (8.6%), and nonurticarial rashes, 5 episodes (1.6%). In order of frequency, the NSAIDs most commonly involved were acetylsalicylic acid (128 instances, 40.3%), dipyrrone (82, 25.8%), paracetamol (24, 7.6%), diclofenac (22, 6.9%),

Table 2. Clinical Characteristics of Patients With NSAID-Induced Cross-Reactive Reactions.*

Challenge Reaction	No. of Patients (%)	Associated Underlying Disease	Atopy	SBPCOC (positives/ negatives)
Nasoocular reaction	8 (5.3)	Rhinitis and/or asthma (100%)	69.2%	42/90
Asthmatic reaction with/without nasoocular reaction	18 (12)			
Periorbital angioedema with asthmatic reaction and/or nasoocular reaction	14 (9.3)			
Isolated periorbital angioedema	51 (34)	Rhinitis and/or asthma (100%)	100%	58/81
Urticaria/ angioedema	59 (39.3)	Chronic urticaria (21.0%)	10.1%	60/135
Total	150	76.6%	54.0%	160/306

*NSAID indicates nonsteroidal anti-inflammatory drug; SBPCOC, single-blind, placebo controlled oral challenge.

propyfenazone (19, 6.0%), ketoprofen (10, 3.1%), and a more heterogeneous group of NSAIDs (ibuprofen, clonixin, naproxen, piroxicam, indomethacin and ketorolac) which was involved in the 32 remaining episodes.

Controlled Oral Challenge

During the study, 697 SBPCOCs were carried out in 223 patients. Five hundred ten showed a negative and 187 a positive outcome (see Tables 2 to 4). In order of frequency, acetylsalicylic acid (in 58 cases, 31.0%), diclofenac (in 51, 27.2%), piroxicam (in 35, 18.7%), dipyron (in 23, 12.3%), paracetamol (in 12, 6.4%), ibuprofen (in 7, 3.7%) and meloxicam (in 1 case) were involved in positive SBPCOCs.

One hundred seventy four patients had a positive response during SBPCOC. Of these, 129 (57.8%) had no type of cutaneous reaction during SBPCOC; 26 (11.6%) only respiratory reactions, 16 (7.2%) both respiratory and skin reactions simultaneously, and 3 had anaphylaxis.

SBPCOC in Patients With Cross-Reactive NSAID-Induced Reactions

Of 150 patients, 59 (39.4%) had urticaria/angioedema, 51 (34%) had periorbital angioedema, 18 (12%) had an asthmatic reaction with or without a nasoocular reaction, 14 (9.3%) had periorbital angioedema associated with some respiratory reaction (8 with an asthmatic reaction and 6 with nasoocular reaction) and 8 (5.3%) had only a nasoocular reaction. Of the total population, 103 (68.7%) were females and 47 (31.3%) were males. The age range was from 5 to 49 years (mean age 29.4 years). The clinical characteristics of each subset of these patients with cross-reactive reactions are summarized in Table 2.

One hundred fifteen patients (76.6%) had some type of associated underlying diseases, although this association was different in each subset of patients. Rhinitis and/or bronchial asthma was diagnosed in all patients with challenge-induced respiratory symptoms and those with isolated periorbital angioedema. Moreover, of the 110 patients with cutaneous reactions exclusively, 24 (21%) had chronic urticaria as underlying disease, but the remaining 86 patients experienced the skin reactions only after taking NSAIDs.

A significant increase in atopy was found exclusively among patients with periorbital angioedema, in comparison with the other skin reactors (100% vs 10.1%, $P < .001$, χ^2 test).

SBPCOC in Patients With Selective NSAID-Induced Reactions

Sixty one patients (29.1%) had selective reactions caused after specific NSAID intake. As shown in Table 3, forty nine (80.3%) had clinical evidence of anaphylaxis and were admitted to the ER, 11 (18%) had urticaria and 1 patient had anaphylaxis when SBPCOCs were carried out. Of the total population, 51 (83.6%) were females and 10 (16.4%) were males. The age ranged from 12 to 78 years (mean age 34.1 years).

In the first subset of 49 patients, tolerance to at least one potent COX-1 inhibitor NSAID was demonstrated, after completing the SBPCOC protocol, except to those NSAIDs reported as being responsible for the previous anaphylaxis or those which were structurally related. The second subset consisted of 11 patients who developed urticaria after SBPCOC with specific NSAIDs; and the remaining patient, who reported a previous dipyron-induced urticaria, experienced anaphylaxis during SBPCOC with this specific NSAID, with tolerance to a potent COX-1/COX-2 inhibitor NSAID (aspirin).

Table 3. Clinical Characteristics of Patients With NSAID-Induced Selective Reactions.*

Challenge Reaction	No. of Patients (%)	Associated Underlying Disease	Atopy	SBPCOC (positives/negatives)
Nil	49 (80.3)	None (78.7 %)	21.3 %	0/178
Urticaria	11 (18.0)			12/16
Anaphylaxis	1 (1.7)			
Total	61		21.3 %	12/194

*Nil indicates that the single-blind, placebo controlled oral challenge (SBPCOC) with the nonsteroidal anti-inflammatory drug (NSAID) involved in the previous reaction was not performed.

The drugs involved in these selective reactions were dipyron in 40 patients (65.6%), propyfenazone in 11 (18.0%), diclofenac in 7 (11.4%), acetylsalicylic acid in 1, and paracetamol in 2 patients. Thirteen cases had allergic rhinitis, but most patients (78.7%) had no evidence of any associated underlying disease.

SBPCOC in Patients With Miscellaneous Reactions

Twelve patients with positive response during SBPCOC could not be included in any of the above mentioned group of syndromes. Of these, 10 were females (83.4%) and 2 (16.6%) were males, with ages ranging from 23 to 45 years (mean age 34.1 years).

Of the 12 patients, 8 (66.8%) had cross-reactive non-urticarial exanthems; two atopic patients had ibuprofen-induced oropharyngeal pruritus, urticaria and asthmatic reactions, but tolerated aspirin in SBPCOC; and two other patients had a systemic reaction clinically indistinguishable from the above mentioned anaphylaxis. Of this group, the first patient, who reported an aspirin-induced urticaria, had a systemic reaction (urticaria, facial angioedema and systolic hypotension) after the intake of 250mg of ibuprofen during SBPCOC. The second patient reported a previous cutaneous and respiratory reaction caused by aspirin. He developed facial and laryngeal edema with intense respiratory distress after administration of 25mg of diclofenac.

Discussion

We studied a large group of patients with challenge-proven NRC and established 4 types of reactions, namely NCR types 1 to 4, according to the clinical syndrome that occurred during controlled oral challenge, the pattern of reactivity among NSAIDs and the existence of other underlying diseases [1] (Table 4).

In our opinion, NRC constitutes a family of diseases that could be initially divided into two groups designated selective and cross-reactive (or multiple) syndromes. The selective group reacted exclusively to NSAIDs involved in the historical

reaction, whereas cross-reactive (or multiple) syndromes occurred in patients who reacted to at least one potent COX-1/COX-2 inhibitor, which was neither involved in previous reactions nor chemically related.

Thus, our NRC type 1, also known as aspirin sensitive asthma [2,10], included 40 patients who exhibited an asthmatic and/or nasooocular reaction, and even periorbital angioedema as part of this upper respiratory reaction in at least 30% of cases [1] during SBPCOC. It is a well defined syndrome characterized by the existence of moderate-to-severe bronchial asthma and rhinosinusitis with or without nasal polyposis [2]. There is evidence to suggest that some patients with challenge-proven NRC type 1 condition may only show isolated nasooocular reaction in subsequent challenges [13,14]. In fact, the nasooocular and asthmatic reactions could be different stages within the natural history of the same inflammatory disease [15]. Almost all patients with NRC type 1 are also sensitive to other NSAIDs [1,2,6] (multiple reactor status), and this capability is related to their potency as COX-1 inhibitors [6]. The disease was first described in the 1920s, but much work has been done to further characterize its genetic [16,17], immunologic [18] and clinicopathologic features [2]. To date, NRC type 1 remains the model of the multiple reactor NRC syndrome with associated underlying disease.

We have also described a group of 59 patients who developed cross-reactive urticaria and/or angioedema during SBPCOC, our NRC type 2. There is now convincing clinical evidence [19] to distinguish at least 2 subsets within this patient group. It has been shown that NSAIDs may cause acute episodes of urticaria/angioedema only when patients are exposed to these drugs [1,19], but they may also aggravate an underlying chronic urticaria/angioedema [9,19]. Some consistent data are now available on the natural history of both subsets of skin reactors [19]. Once a susceptible, but otherwise healthy subject develops urticaria/angioedema after taking NSAIDs, two possibilities may occur: patients may continue with the same reaction pattern throughout their life; or the NSAID reaction may precede the onset of episodes of chronic urticaria [19]. Moreover, 30% of patients with chronic urticaria develop hives after ingesting NSAIDs [9], and studies have shown that there is a positive correlation between the disease

Table 4. Clinical Patterns of NSAID-Induced Reactions.*

NSAID Reactivity Pattern	Clinical Form	Associated Underlying Diseases
Cross-reactive syndromes	Type 1 Nasoocular and/or asthmatic reaction	Rhinitis and/or bronchial asthma with or without nasosinusual polyposis
	Type 2 Urticaria y/o angioedema	Chronic urticaria/angioedema
	Type 3 Isolated periorbital angioedema	Atopic disease (rhinitis and/or bronchial asthma and NSAID-sensitivity mite ingestion reaction syndrome)
Selective syndromes	Type 4 Systemic anaphylaxis and urticaria	None
Miscellaneous syndromes	Overlap reaction: Selective reaction (oral allergy syndrome-like, urticaria and asthma) in patients with atopic disease (rhinitis and/or bronchial asthma)	
	Non-urticarial reaction: Cross-reactive macular and/or papular exanthems	
	Systemic reaction: Cross-reactive anaphylaxis-like reaction in some cases of type 1 and type 2 patients during challenge with potent COX-1/COX-2 inhibitors	

* NSAID indicates nonsteroidal anti-inflammatory drug; SBPCOC, single-blind, placebo controlled oral challenge; COX, cyclooxygenase.

activity and the likelihood of developing NSAID reactions among these patients [20].

The third group, our NRC type 3, included 51 patients who presented isolated periorbital angioedema, often bilateral in nature, after challenge. There were certain characteristics that distinguished this syndrome as a distinct entity: Firstly, it was commonly seen in pediatric and juvenile patients [1,12]. Secondly, most of these patients exhibited cross-sensitivity with other NSAIDs; and thirdly, an underlying dust mite sensitization was always seen [21]. Patients with challenge-proven aspirin-induced asthma had positive wheal and flare skin tests to relevant allergens in a third of cases [22] and it has been shown that atopic disease is significantly associated with a positive SBPCOC to NSAIDs [23]. It is even possible that atopy or specific responses to certain allergens [24] may predispose patients to some NRC syndromes [21], such as NRC type 3 or the infantojuvenile form.

All patients with clinical evidence of anaphylaxis at entry were included in the NRC type 4 group. We also observed that certain patients with selective NSAID-induced urticaria can develop selective systemic reactions in subsequent exposures to specific NSAIDs [3,4], even during SBPCOC [1]. For this reason, a group of 11 patients with urticaria who were clinically indistinguishable from NRC type 2, except for being selective reactors, were also included in the NRC type 4 category. Most patients with systemic anaphylaxis or selective urticaria were apparently healthy

subjects. All NSAIDs appear capable of causing such selective reactions [25], but pyrazol and acetic derivatives were the most common drugs involved in our population [1,4,5]. Recently, an unexpectedly high relative risk for developing anaphylactic reactions during the use of acetic and propionic derivatives has been reported [26]. This NRC type 4 remains the model of selective reactor, non-disease associated, NRC syndrome. Probably, an IgE-mediated mechanism underlies this type 4, as recently demonstrated with propyfenazone [8].

Despite the diverse nature of these NRC diseases, their clinical pattern is remarkably consistent. However, a few patients cannot be included accurately in any of the above mentioned categories. Some have clinical features common to NRC types 1 (bronchial asthma) and 4 (selective urticaria), and may constitute a separate group (an overlap reaction), as other authors have also suggested [10,11,27]. Other patients showed non-urticarial exanthems or a systemic response during SBPCOC with a multiple reactivity pattern among NSAIDs. There is some evidence that this cross-reactive variant of systemic anaphylaxis may be a common pathway of several cross-reactive types of NRC when potent COX-1/COX-2 inhibitors were used in SBPCOC [1,28]. However, more data on these patients need to be collected to unequivocally determine if they constitute distinct NRC types.

In conclusion, we have clinically characterized a large population of patients with NSAID-induced reactions by

means of controlled oral challenges, and we have proposed a working classification of this NRC. Patients showed 4 well defined types of reaction which were recognized through the clinical features and the SBPCOC results.

Acknowledgments

Supported by grants from the Fondo de Investigación Sanitaria (96/0685), Fundación de la Sociedad Española de Alergología e Inmunología Clínica (ATD-95) and Instituto de Salud Carlos III (Vegetalia, ISCIII-RTIC-G03/094, and RedRespira, ISCIII-RTIC-C03/011).

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■ *Manuscript submitted September 29, 2006; accepted December 11, 2006.*

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