

Anaphylactoid reactions due to nonsteroidal antiinflammatory drugs: clinical and cross-reactivity studies

J Quiralte, MD; C Blanco, MD; R Castillo, MD; Nancy Ortega, MD; and Teresa Carrillo, MD, PhD

Background: Anaphylactoid reactions due to nonsteroidal antiinflammatory drugs have been described.

Objective: To study the clinical characteristics of 21 patients with anaphylactoid reactions due to nonsteroidal antiinflammatory drugs and to determine the cross-reactivity to non-steroidal antiinflammatory drugs not involved in the previous reactions nor structurally related by means of single-blind, placebo-controlled drug challenges.

Patients and methods: Twenty-one patients who exhibited clinical evidence of anaphylactoid reactions after nonsteroidal antiinflammatory drugs were recruited for the study at the time of admission in Emergency Unit of our Hospital. Single-blind, placebo controlled oral challenges with nonsteroidal antiinflammatory drugs (except those reported by the patient as being responsables for the previous reaction), were performed in all patients.

Results: Fifteen patients were woman and six man, with a mean age of 35.7 years (range 18 to 62 years). Thirteen patients (60%) were normal subjects without concomitant diseases. No increase in frequency of atopy in comparison to the general population was observed. Pyrazole derivatives were the most common nonsteroidal antiinflammatory drugs involved (71.3%). A tolerance to drugs included in drug challenge protocol was noted in all patients.

Conclusion: In our population, pyrazole derivatives were the most common nonsteroidal antiinflammatory drugs involved in anaphylactoid reactions. Most patients appeared to be otherwise normal subjects without concomitant disease and no cross-reactivity with other non-steroidal antiinflammatory drugs not involved in the anaphylactoid reaction nor structurally related was found.

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INTRODUCTION

Drugs are the most common cause of anaphylaxis.¹ In different epidemiologic surveys, nonsteroidal antiinflammatory drugs are among the most frequently encountered drugs.^{2,3} Little, however, is known about anaphylactoid reactions due to nonsteroidal antiinflammatory drugs. Several reports

focused on this specific adverse reaction have delineated peculiar clinical characteristics in these patients⁴⁻⁶ in relation to other subjects with nonsteroidal antiinflammatory drug sensitivity.^{6,7} These observations are complicated by several confounding factors: first, small patient groups are usually studied⁸⁻¹⁹; second, the definition of anaphylactoid reaction is quite different among studies and the authors do not differentiate between mucocutaneous signs^{5,16} and the existence of others such as cardiovascular, respiratory, and gastrointestinal signs or symptoms^{12,19}; third, the information about concomitant diseases (specifically, atopic diseases) exhibited by the patients is scarce; and fourth, although

controlled oral challenges have been performed in patients with anaphylactoid reactions,⁵ the challenges are limited because of the risk of life-threatening reactions.

Consequently, we developed a study that considered all these difficulties. First, we identified patients with clinical evidence of anaphylactoid reactions after nonsteroidal antiinflammatory drug administration upon admission to the hospital. Then we prospectively studied the administration of nonsteroidal antiinflammatory drugs that were neither involved in the previous reactions nor structurally related by means of single-blind placebo-controlled drug challenges (SBPCDC).

METHODS

Patients

Twenty-one patients exhibiting clinical evidence of anaphylactoid reaction after nonsteroidal antiinflammatory drug administration upon admission to the emergency unit of our Hospital from 1992 through 1995 were recruited for the study. Anaphylactoid reaction was defined as the presence of urticaria and/or angioedema plus hypotension (systolic blood pressure below 90 mmHg) and/or laryngeal edema.

The following data were collected for all the patients: age, sex, and concomitant diseases, as well as those data related to the clinical characteristics of anaphylactoid reactions at time of admission: nonsteroidal antiinflammatory drug involved, dose and elapsed time between administration of the drug, and beginning of the reaction, symptoms, and previous reactions related by the patient. Subjects were diagnosed as being atopic if they met the following criteria: (1) rhinitis, conjunc-

Sección de Alergia, Hospital Universitario Ntra. Sra. del Pino C/ Angel Guimerá 93, 35005-Las Palmas de Gran Canaria, Spain.

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tivitis, and/or bronchial asthma, (2) skin prick wheal of 3 mm greater than negative control to one or more of house dust mites, fungi, animal danders, or pollen extracts (Laboratorio Ifidesa-Arístegui S.A, Bilbao, Spain) and (3) specific IgE values >0.7 KU/L measured by Pharmacia ImmunoCap System (Pharmacia Diagnostics, Sweden).

None of the patients had suffered episodes of urticaria/angioedema at any time in the past week prior to controlled oral challenge and FEV₁ values were at least 80% of predicted, with an absolute value >1.5 L. Hourly measurements of peak expiratory flow rate (PEF) with a mini-Wright peak flow meter (Clement Clarke International Ltd, London, England) during the day prior to challenge, showed a variability less than 20% in PEF values in all subjects. Antihistamines, cromolyn, and inhaled sympathomimetic agents were stopped 48 hours before the challenge. Written informed consent from the patients was necessary to participate in the study and the protocol was approved by the Investigation and Ethics Committees of the Hospital.

Controlled Oral Challenge

Patients were included in a previously established SBPCDC protocol, at least 1 month after resolution of the anaphylactoid reaction. The dosing protocol for the SBPCDCs is summarized in Table 1. Nonsteroidal antiinflammatory drugs involved in the anaphylactoid reactions and other structurally related drugs were excluded from SBPCDCs. Each SBPCDC was carried out separately on different days, with at least 7-day intervals between successive challenges. Each patient was challenged with the first drug (including placebo) not involved in the previous reaction. If no response occurred (ie, no evidence of reaction), successive SBPCDCs with the next drugs were performed. After a positive SBPCDC, the challenge procedure was interrupted. SBPCDC was considered positive if it fulfilled at least one of the following criteria: (1) a 20% fall in FEV₁; (2) nasoocular reaction: sneezing, rhinorrhea, nasal blockage, and conjunctival injection; (3) cutaneous

Table 1. Drugs and Doses* Used for Single-Blind Challenges

	Dose
Lactose	
Paracetamol	100, 250, 500 mg†
Salsalate	500, 1000 mg†
Diflunisal	100, 500 mg†
Mefenamic acid	50, 125, 250 mg†
Diclofenac	25, 50 mg‡
Piroxicam	10, 20 mg‡
Ketoprofen	10, 25, 50 mg‡
Dipyrone	10, 50, 125, 250, 575 mg†
Acetylsalicylic acid	50, 100, 250, 500 mg§¶

* All the drugs and placebo were administered in opaque gelatin capsules with † 60-minute, ‡ 120-minute, or § 180-minute intervals between doses.

|| Four doses (10, 50, 125, and 250 mg) were administered on the first day, and 575 mg on the second day.

¶ Two doses (50 and 100 mg) were administered on the first day and the other two doses (250 and 500 mg) on the second day.

rash of any morphology; (4) swelling of skin and/or external mucosa; and (5) anaphylactoid reaction: urticaria and/or angioedema plus hypotension (a 30 mmHg decrease in systolic blood pressure) and/or laryngeal edema. During the challenge procedure, blood pressure was monitored as well as the FEV₁ values (15 minutes, 30 minutes, and every hour after administering each drug or placebo dose or at any time when other symptoms were reported by the patient).

RESULTS

Patients

As shown in Table 2, the 21 patients with anaphylactoid reaction due to nonsteroidal antiinflammatory drugs included 15 women and 6 men ranging in age from 18 to 62 years (mean age 35.7 years). Six of the 21 patients had experienced definite reactions to nonsteroidal antiinflammatory drug on previous occasions before being included in the study (Table 3). Anaphylactoid reaction was the most common previous reaction. Symptoms that appeared during admission involved the skin (urticaria, angioedema) in 21 pa-

tients, the respiratory tract (nasal congestion, conjunctival injection or wheezing) in 10, the gastrointestinal system (mainly abdominal pain) in 2, hypotension in 6, and laryngeal edema in 15. Drugs involved in anaphylactoid reactions were dipyrone in 12 patients (57.1%), propyphenazone in 3 (14.2%) and acetic derivatives such as diclofenac and indomethacin in 3 (14.2%). Other nonsteroidal antiinflammatory drugs (see Table 4) were involved in the remaining patients.

Six patients suffered allergic rhinoconjunctivitis and two, bronchial asthma. The remaining patients had no evidence of any concomitant diseases. Factors that likely increased the risk of anaphylactoid reaction, as for example betablocker use,²⁰ were not identified.

Controlled Oral Challenge

During the study, 155 SBPCDC were carried out in 21 subjects (Table 4). In 18 patients, a tolerance to all the drugs after completing SBPCDC protocol (except those reported as being responsible for the anaphylactoid reaction) was noted. The remaining three patients did not complete the protocol (patients 7, 14, 16), but some other major nonsteroidal antiinflammatory drugs (acetyl salicylic acid, dipyrone, diclofenac, and ketoprofen) were administered during challenge and tolerated.

DISCUSSION

We prospectively conducted SBPCDCs with nonsteroidal antiinflammatory drugs in 21 patients who presented clinical evidence of anaphylactoid reactions after nonsteroidal antiinflammatory drug administration at the time of hospital admission. On the basis of these documented systemic manifestations, we precluded the use of nonsteroidal antiinflammatory drugs involved in the anaphylactoid reactions during SBPCDCs, because life-threatening events may occur. Thus, we used an alternative approach for the study of these reactions that consisted of challenging with other non-structurally related nonsteroidal antiinflammatory drugs.

Although our sample size is too small to draw any definite conclusions,

Table 2. Clinical Characteristics of the Patients with Anaphylactoid Reactions*

Patient	Sex	Age, yr	Atopy	Concomitant Disease	Drug Involved†	Symptoms†
1	F	30			Ind	U/AE/LE/RC
2	F	42			Dip	U/H
3	M	21	HDM	RC	ASA	U/AE/LE/RC/A
4	M	21	Cat	RC	Prop	U/AE/LE/A
5	M	62			Dip	U/AE/H
6	F	34	HDM	RC	Dip	U/LE/A
7	F	49	Pollen	RC	Glafl	U/AE/LE
8	F	28			Prop	U/AE/LE
9	M	61			D	U/AE/H
10	F	25	Cat	R	Dip	U/AE/H
11	F	27	HDM	R + A	D	U/AE/LE/A
12	F	52	HDM	R + A	P	U/AE/H
13	F	33			Dip	U/AE/LE/A
14	F	60			Dip	U/AE/LE/AP
15	M	18	HDM	R	Dip	U/H/LE/A
16	F	36			Dip	U/LE
17	M	22			Prop	U/AE/LE
18	F	33			Dip	U/AE/LE/AP
19	F	20			Dip	U/H/A
20	F	40			Dip	U/AE/LE/A/RC
21	F	37			Dip	AE/LE/A

* F, female; M, male; HDM, house dust mites; R, rhinitis; RC, rhinoconjunctivitis; A, asthma; Ind, indomethacin; Dip, dipyrone; ASA, acetylsalicylic acid; Prop, propyphenazone; Glafl, Glafenine; D, diclofenac; P, paracetamol; U/AE, urticaria/angioedema; LE, laryngeal edema; H, hypotension; and AP, abdominal pain.

† Symptoms on admission to the emergency room, and drug involved in the reaction.

Table 3. Previous Reactions to Non-Steroidal Antiinflammatory Drugs in the Patients

Patient	Adverse Reaction/ Drug Involved
3	Anaphylactoid reaction/ acetylsalicylic acid
4	Angioedema/Propyphenazone Angioedema, urticaria/ propyphenazone Anaphylactoid reaction/ propyphenazone*
6	Urticaria/dipyrone
9	Anaphylactoid reaction/ aceclofenac
17	Urticaria/dipyrone
18	Urticaria/dipyrone Anaphylactoid reaction/ propyphenazone*

* On two separate occasions.

anaphylactoid reactions were more common in women and were associated mainly with pyrazole derivatives. Nonsteroidal antiinflammatory drugs as a group have been associated with an increased relative risk for anaphy-

lactoid reactions.² Previous suggestions that the use of tolmetin and zomepirac was associated with a higher risk of anaphylactoid reactions could not be confirmed in recent surveys.^{2,21} A cohort study of the treatment of colic in general practice showed that serious events, most likely due to adverse reactions to analgesics, were bronchial asthma and anaphylactoid reactions. The incidence was about 2 in 1000 treated cases. The relative risk was not increased by treatment with pyrazole derivatives.²²

In the literature reviewed (Comprehensive Medline 1983–95) we have found that nonsteroidal antiinflammatory drugs involved in anaphylactoid reactions belonged to different chemical groups: pyrazole,⁴ anthranilic,^{12,13} acetic^{3,8–11} and propionic^{14,15} derivatives, paracetamol,¹⁶ and salicylates.^{17–19} Possibly, the availability of NSAIDs, specific guidelines of regulatory drug agencies, and prescribing habits of physicians in restricted geographic areas could explain the pre-

dominance of certain nonsteroidal antiinflammatory drugs as causes of anaphylactoid reactions, rather than intrinsic properties of the specific drugs.

Nonsteroidal antiinflammatory drug sensitivity usually coexists with an underlying disease, rhinosinusitis and/or bronchial asthma,²³ and chronic urticaria.²⁴ Sixty percent of our patients appeared to be otherwise normal. The remaining patients were atopic; but no increase of atopy was found when compared with a random population in our geographic area, the Canary Islands (Spain), a subtropical land at sea level.²⁵ Recently, Bochenek et al have demonstrated an association of atopic trait with nonsteroidal antiinflammatory drug sensitivity (mainly bronchial asthma, urticaria, and systemic anaphylaxis).²⁶ This finding contrasts with the prevalence of atopy found in our previously reported population of nonsteroidal antiinflammatory drug reactors,⁶ in which only patients with isolated periorbital angioedema and respiratory manifestations (rhinoconjunctivitis and/or bronchial asthma) showed an increase in prevalence of atopy.

Patients with nonsteroidal antiinflammatory drug sensitivity also react to other nonsteroidal antiinflammatory drugs, and this capability is related to their potency as inhibitors of cyclooxygenase.⁷ Patients showed no cross-reactivity with other nonsteroidal antiinflammatory drugs not structurally related even those that are potent inhibitors of cyclooxygenase activity in vitro.⁷ This selective pattern has also been described in some cases of localized periorbital angioedema,^{5,6,27,28} urticaria, and anaphylactoid reaction.^{4,5} This evidence would indicate that cyclooxygenase inhibition cannot be implicated in these NSAID induced reactions, however we have not elucidated the mechanism involved at present.

Patients with anaphylactoid reactions due to nonsteroidal antiinflammatory drugs exhibited a markedly different clinical profile in relation to other nonsteroidal antiinflammatory drug reactors: most patients appeared to be otherwise normal subjects, pyrazole derivatives were the most

Table 4. Single-Blind, Placebo-Controlled Drug Challenges Performed in Patients with Anaphylactoid Reaction

Patient	SBPCDCs*
1	P, S, Dif, Dip, M, Pi, K, ASA
2	P, S, Dif, M, D, Pi, K, ASA
3	P, S, Dif, Dip, M, D, Pi, K
4	P, S, Dif, M, D, Pi, K, ASA
5	P, S, Dif, M, D, Pi, K, ASA
6	P, S, Dif, M, D, Pi, K, ASA
7	P, Dip, ASA
8	P, S, Dif, M, D, Pi, K, ASA
9	P, S, Dif, Dip, M, Pi, K, ASA
10	P, S, Dif, M, D, Pi, K, ASA
11	P, S, Dif, Dip, M, Pi, K, ASA
12	S, Dif, Dip, M, D, Pi, K, ASA
13	P, S, Dif, M, D, Pi, K, ASA
14	P, S, Dif, D, Pi, K, ASA
15	P, S, Dif, M, D, Pi, K, ASA
16	ASA
17	P, S, Dif, M, D, Pi, K, ASA
18	P, S, Dif, M, D, Pi, K, ASA
19	P, S, Dif, M, D, Pi, K, ASA
20	P, S, Dif, M, D, Pi, K, ASA
21	P, S, Dif, M, D, Pi, K, ASA

* S, salsalate; Dif, diflunisal; M, mefenamic acid; D, diclofenac; Pi, piroxicam; K, keto-profen; Dip, dipyrone; ASA, acetylsalicylic acid; Ind, indomethacin; Pr, propyphenazone; and Glaf, glafenine.

common nonsteroidal antiinflammatory drugs involved, and no cross-reactivity among nonsteroidal antiinflammatory drugs that were not involved in the anaphylactoid reaction or structurally related was found. Based on current experience, tolerance to particular nonsteroidal antiinflammatory drugs during SBPCDC will indicate a safe alternative in patients with anaphylactoid reactions.

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Request for reprints should be addressed to:
Joaquín Quiralte, MD
Sección de Alergia
Hospital Universitario Nuestra Señora del Pino
C/ Angel Guimera 93
35005-Las Palmas de Gran Canaria
Spain