

Original articles

Intolerance to piroxicam in patients with adverse reactions to nonsteroidal antiinflammatory drugs

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To evaluate the tolerance to piroxicam in patients with urticaria induced by analgesic and/or nonsteroidal antiinflammatory drugs (NSAIDs), we carried out a 2-year study in an outpatient clinic. All the patients referred to the clinic for study entered a protocol for evaluation of intolerance to one or more drugs. If patients were allergic to at least two different NSAIDs they were allocated to group A, but if patients were allergic to only one they were considered as having selective intolerance (group B). Either piroxicam or placebo was administered under controlled conditions to both groups. In group A, five out of 18 patients had a positive response to piroxicam. In group B, in all the 25 cases studied a good tolerance to piroxicam was shown. These results indicate that in the group with intolerance to NSAIDs piroxicam induced a positive reaction in 27% of the cases, and that this drug should be administered with caution and with a previous controlled challenge in this type of patient. Piroxicam was well tolerated in the group with selective intolerance, indicating that mechanisms other than interference with the prostaglandin synthesis and release of inflammatory mediators participate in allergic reactions to NSAIDs. (*J ALLERGY CLIN IMMUNOL* 1992;90:873-9.)

Key words: Piroxicam, NSAID, intolerance, adverse reactions

Patients with acetylsalicylic acid (ASA) intolerance usually have nonimmunologic cross-reactivity with other antiinflammatory drugs.^{1, 2} This phenomenon has generally been classified as intolerance to nonsteroidal antiinflammatory drugs (NSAIDs). All potential inhibitors of prostaglandin synthesis may have the capacity to induce adverse reactions in patients sensitive to ASA. In some instances the first drug that induces the reaction may be different from ASA, but when challenged, the patients also have an intolerance to other NSAIDs including ASA.¹⁻³ Different clinical entities have been reported on cross-intolerance to NSAIDs.³ An important number of persons have

TABLE I. Drugs and incremental doses used for challenging

Piroxicam		5	20
Paracetamol	125	250	500
Diclofenac	5	50	100
Diflunisal		125	375
Mefenamic acid		60	250
Glafenine	10	50	200
Dipyrone	5	150	450
Propiphenazone		25	275
Ketoprofen		12	50
Indomethacin		5	25
ASA	50	200	500

Doses expressed in milligrams. In the case of paracetamol, diclofenac, glafenine, dipyrone, and ASA three doses were used.

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mainly respiratory problems, but in another significant group urticaria and/or systemic manifestations without pulmonary involvement may occur.^{1, 3}

Piroxicam is an antiinflammatory drug used worldwide.⁴ Its ability to interfere with the synthesis and release of inflammatory mediators has been reported

TABLE II. Cases with intolerance to NSAIDs (group A)

Patient	Age	Sex	Clinical manifestations	Drug involved	Elapse time
1	34	F	Angioedema	ASA + pirazolone	90 min
			Angioedema	ASA	1 hr
2	47	F	Urticaria	ASA	1 hr
3	60	F	Angioedema	ASA	6 hr
			Angioedema	Pirazolone	6 hr
4	50	M	Urticaria	ASA	6 hr
5	60	F	Urticaria	ASA	1 hr
6	57	M	Urticaria	Indomethacin	1 hr
			Urticaria	Ketoprofen	1 hr
7	47	F	Urticaria	ASA	20 min
8	62	F	Urticaria	Pirazolone	3 hr
			Urticaria	ASA	4 hr
9	38	M	Exanthema	ASA	90 min
10	53	M	Urticaria	ASA	2 hr
			Urticaria	Dipyrone	1 hr
11	45	M	Angioedema	ASA	2 hr
			Angioedema	Indomethacin	3 hr
12	28	F	Urticaria	ASA + paracetamol	90 min
13	27	F	Urticaria	ASA	3 hr
14	47	M	Urticaria	ASA	45 min
15	62	M	Urticaria	ASA	2 hr
			Urticaria	Dipyrone	3 hr
16	37	F	Urticaria	ASA	90 min
			Urticaria	Dipyrone	120 min
17	63	M	Urticaria	ASA	20 min
18	35	M	Angioedema	ASA	5 hr

Elapse time is the time interval reported by the patient between the administration of the drug and the appearance of the symptoms.

in several experimental and human systems.⁵⁻⁹ As a prostaglandin synthetase inhibitor it can cross-react and induce reactions in cases of intolerance to NSAIDs.^{3,5} Preliminary data from our group indicated that piroxicam is able to induce urticaria in patients with intolerance to NSAIDs.¹⁰ In this study we selected a group of patients with urticarial or immediate cutaneous and/or systemic manifestations to different NSAIDs and determined the tolerance to piroxicam. Results show that this drug may induce reactions in cases with intolerance to NSAIDs and emphasize that this drug should not be administered to patients with intolerance to NSAIDs unless a previous controlled challenge is made.

MATERIAL AND METHODS

Over a period of 2 years all the patients referred to our clinic as having intolerance to any antiinflammatory drug entered a protocol to evaluate if they belonged to the group with intolerance to NSAIDs (group A) or intolerance to one single drug (group B). When the patients were classified according to the criteria described below, a controlled challenge with piroxicam was carried out.

Controlled challenges

A single-blind challenge was conducted, and all or several of the following drugs were included in the protocol including placebo: paracetamol (acetaminophen), mefenamic acid, glafenine, dipyrone, propiphenazone, ASA, ketoprofen, and fructose. Not all the cases required the administration of all the drugs for inclusion in the study. Different concentrations were used for challenging until therapeutic doses were reached. There was a 1-hour interval between each dose, and if no response appeared, the next dose was administered. The concentrations of the different drugs used are presented in Table I. Maximum dosage was the following: piroxicam 20 mg, paracetamol 500 mg, diclofenac 100 mg, diflunisal 375 mg, mefenamic acid 250 mg, glafenine 200 mg, dipyrone 450 mg, propiphenazone 275 mg, ketoprofen 50 mg, indomethacin 25 mg, and ASA 500 mg.

When the patients were allergic to at least one other drug in addition to the one involved in the reaction they were considered as belonging to group A. When a positive response by challenge to only one drug developed in the patients and they had good tolerance to the other nine included in Table I, they were classified as having selective intolerance (group B). Only cutaneous manifestations were included in the study. All cases with respiratory manifestations

TABLE III. Cases with intolerance to NSAIDs (Group A), challenge results

Patient	Drug challenge results	Elastp time	Clinical manifestations
1	Parac(-), mefe(-), ketop 50 mg	30 min	Urticaria/angioedema
2	Parac(-), mefe(-), diel 100 mg	30 min	Urticaria
	dip 450 mg	90 min	Urticaria/angioedema
3	Parac(-), glaf 200 mg	6 hr	Angioedema
	mefe 250 mg	6 hr	Urticaria
4	Mefe(-), glaf(-), dip(-), indo 25 mg	4 hr	Urticaria/angioedema
5	Glaf(-), mef(-), dip(-), ketop(-), indo 25 mg	1 hr	Pruritus/exanthema
6	Parac(-), mefe(-), glaf 200 mg	90 min	Urticaria
	dip (-), indo 25 mg	1 min	Urticaria
	ketop 50 mg	1 hr	Urticaria
7	Parac(-), indo(-), ASA 200 mg	30 min	Exanthema/angioedema
8	Parac(-), glaf(-), mefe 250 mg	90 min	Urticaria
9	indo 25 mg	1 hr	Urticaria
	dip 450 mg	1 hr	Urticaria
10	Parac(-), mefe 250 mg	1 hr	Urticaria
11	Parac(-), dip(-), ketop 50 mg	3 hr	Angioedema
	indo 25 mg	3 hr	Angioedema
12	Parac(-), mefe 200 mg	8 hr	Urticaria
	dip 450 mg	1 hr	Urticaria
13	Mefe(-), indo 25 mg	4 hr	Urticaria
14	Parac(-), mefe(-), ketop 50 mg	30 min	Urticaria/angioedema
	indo 25 mg	90 min	Urticaria/angioedema
15	Mefe(-), glaf(-), indo 25 mg	3 hr	Exanthema
16	Parac(-), ASA 200 mg	2 hr	Urticaria/angioedema
	ketop 100 mg	2 hr	Urticaria
17	Parac(-), mefe(-), glaf 200 mg	45 min	Urticaria
18	Parac(-), mefe(-), dip(-), indo 25 mg	4 hr	Angioedema

Prop. Propiphenazone; *dip.* dipyrone; *parac.* paracetamol; *diel.* diclofenac; *glaf.* glafenine; *ketop.* ketoprofen; *mefe.* mefenamic acid; *indo.* indomethacin.

Patients 1, 2, 8, 12, 17, and 18 had a positive response after administering piroxicam.

(nasal and/or pulmonary) were excluded. The symptoms described by the patients and the symptoms induced by the controlled challenges were categorized as follows: urticaria for large macular erythematous areas elevated over the skin and spread to different parts of the body; angioedema for swelling of the skin and/or external mucosa; exanthema for small macular areas in different parts of the body; and anaphylaxis when generalized erythema, pruritus, general malaise, and faintness or hypotension or both were associated. The study was approved by the ethics committee of the hospital, and informed consent was given by every patient who participated in the study.

RESULTS

One-hundred twenty-one cases were evaluated in the study. The symptoms reported by the patients were the following: urticaria (60%), angioedema (18%), anaphylactic shock (10%), generalized exanthema

(3%), systemic pruritus with erythema (4%), asthma accompanied by angioedema (2%), and fixed drug eruption (3%). After completing the challenge, 18 cases proved to be intolerant to two or more NSAIDs. These were classified as group A according to the criteria presented in the "Methods" section. In 25 cases only one drug was involved, the patients were tolerant to all the other NSAIDs included in the study (group B). In the remaining 78 cases a good tolerance to all the drugs was obtained, including those reported by the patient as being responsible for the prior reaction episode.

In group A (Table II), nine patients were women and 9 were men. The mean age was 47 years, with a maximum of 63 years (case 17) and a minimum of 27 years (case 13). A total of 26 episodes were reported by the patients. In eight cases the episode oc-

TABLE IV. Patients with intolerance to a single drug (group B)

Patient	Age	Sex	Clinical manifestations	Drug involved	Elaste time
1	30	F	Urticaria	Prop	30 min
2	35	F	Urticaria	Prop	90 min
3	64	M	Anaphylaxis	Dip	30 min
4	40	F	Urticaria	Dip	10 min
5	37	F	Urticaria	Dip	20 min
6	41	M	Urticaria	Dip	6 hr
7	25	F	Urticaria	Parac-dip	20 min
8	28	F	Anaphylaxis	Dip	10 min
9	35	F	Anaphylaxis	Dip	5 min
10	45	F	Urticaria	Dip	5 min
11	62	F	Anaphylaxis	Dip	10 min
12	47	F	Anaphylaxis	Prop	15 min
13	55	M	Urticaria	Dip	10 min
14	45	F	Anaphylaxis	Diclof	15 min
15	60	F	Anaphylaxis	Glaf	10 min
16	50	F	Anaphylaxis	Dip-prop	10 min
			Anaphylaxis	Prop	15 min
17	47	F	Angioedema	Prop	20 min
18	28	F	Exanthema	Diff-dip	15 min
19	50	F	Angioedema	Glaf	5 min
20	37	F	Angioedema	Ketop-ASA	90 min
			Angioedema	ASA	60 min
21	60	M	Anaphylaxis	Dip	5 min
22	50	F	Urticaria	Diclof-ASA	30 min
23	35	F	Urticaria	Dip	45 min
24	37	M	Anaphylaxis	Diclof	10 min
25	35	F	Urticaria	Dip	15 min

curred on two occasions and from different drugs, and 10 cases reported having had only one episode. ASA was involved in 18 episodes, dipyrone in five, indomethacin in two, and ketoprofen in one. When challenged with the different NSAIDs reflected in the protocol (Table III), all the patients in group A responded to at least one other drug apart from the one reported by the patient. Indomethacin was the most frequently involved, being positive in eight challenges, ketoprofen in five, ASA in two, glafenine in three, dipyrone in two, mefenamic acid in four, and diclofenac in one.

In group B 25 cases were included (Table IV). In all except five cases only one drug was involved. In case 7 paracetamol and dipyrone were administered together, in case 16 dipyrone and propiphenazone were administered together in case 18 diflunisal and dipyrone, in case 20 ketoprofen and ASA, and in case 22 diclofenac and ASA. Challenge results (Table V) showed that in all these cases only one drug was responsible for inducing the reaction. According to the challenge results dipyrone was responsible in 12

cases, propiphenazone in five, diclofenac in two, diflunisal in one, ASA in two, and glafenine in two. In all of them good tolerance existed to all the drugs included in Table I, and therefore they were classified as intolerant to a single drug.

Five patients in group A responded to the challenge with piroxicam. Cases 1, 3, 8, and 12 responded to a dose of 20 mg, and case 17 responded to 5 mg. The symptoms induced by challenge were the same as those reported by the patients when they entered the study (Table VI). According to these data piroxicam challenge was positive in 27% of the group A cases. In group B, all the cases had good tolerance to piroxicam.

DISCUSSION

NSAIDs are the pharmacologic agents that most commonly produce allergic drug reactions.¹ The clinical manifestations of intolerance to these drugs include urticaria and angioedema, asthma and nasal polyps, rhinoconjunctivitis, and anaphylaxis.^{1,2} Urticaria and angioedema are considered a different entity from

TABLE V. Patients with intolerance to a single drug (group B), challenge results

Patient	Drug challenge results	Elastpse time	Clinical manifestations
1	Prop 275 mg	15 min	Urticaria
2	Prop 275 mg	60 min	Urticaria
3	Prop 275 mg	40 min	Angioedema
4	Dip 50 mg	30 min	Urticaria
5	Dip 50 mg	10 min	Urticaria/laryngeal angioedema
6	Dip 450 mg	6 hr	Angioedema/systemic pruritus
7	Parac 250 mg	15 min	Urticaria
8	Prop 25 mg	30 min	Systemic pruritus
9	Dip 50 mg	10 min	Anaphylaxis
10	Dip 50 mg	20 min	Anaphylaxis
11	Dip 150 mg	10 min	Anaphylaxis
12	Prop 25 mg	20 min	Pruritus
13	Dip 150 mg	10 min	Urticaria
14	Diclof 5 mg	30 min	Urticaria
15	Glaf 10 mg	15 min	Anaphylaxis
16	Dip 450 mg	10 min	Anaphylaxis
17	Dip 450 mg	30 min	Pruritus
18	Difl 375 mg	10 min	Urticaria
19	Glaf 50 mg	10 min	Laryngeal angioedema
20	ASA 500 mg	2 hr	Angioedema
21	Dip 50 mg	10 min	Anaphylaxis
22	ASA 50 mg	30 min	Urticaria
23	Dip 450	30 min	Urticaria/angioedema
24	Diclof 5 mg	10 min	Anaphylaxis
25	Dip 50 mg	15 min	Anaphylaxis

TABLE VI. Patients with positive challenge to piroxicam (Group A)

Patient	Dose	Elastpse time	Symptoms after provocation
1	20 mg	2 hr	Facial erythema and eyes angioedema
3	20 mg	6 hr	Lips angioedema, urticaria in hands and legs.
8	20 mg	1 hr	Generalized urticaria, eyes angioedema
12	20 mg	2 hr	Generalized urticaria
17	5 mg	30 min	Facial pruritus, lips angioedema.

asthma and nasal polyps, and the association of both processes is uncommon.^{2, 3} The inhibition of prostaglandin biosynthesis by interference with the cyclooxygenase pathway has been proposed as the common mechanism inducing these reactions.^{2, 11} Piroxicam is an NSAID that was first introduced in 1979.⁴ Since then different postmarketing studies have been performed worldwide establishing its efficacy and good tolerance.^{4, 12} It has been reported to be tolerated better

than indomethacin and ASA and as well as naproxen and ibuprofen.¹³

Apart from gastrointestinal effects,^{4, 14} the most frequent adverse reaction reported so far is photosensitivity.¹⁵⁻¹⁷ Other adverse reactions are Lyell's syndrome and acute hepatitis.^{18, 19} To our knowledge no manifestations of urticaria, anaphylactic shock, and/or precipitation of asthmatic attacks induced primarily by this drug have been reported so far. Thus

we decided to study the cross-sensitivity between piroxicam and other NSAIDs.

The comparison of the prostaglandin synthesis inhibitory activity with other drugs ranks piroxicam as a potent agent.⁵ It has been reported to be a selective inhibitor of the cyclooxygenase pathway with little activity on the phospholipase, thromboxane, prostacyclin synthetase, and lipoxygenase.^{6,7} Accordingly, our objective was to determine the tolerance in a group with proved intolerance to NSAIDs.

Since there are discrepancies in the mechanism of respiratory and urticarial manifestations,^{1,2,20} and the groups with urticaria are defined as a different population,² we selected a group with urticarial problems for this study. Furthermore, in the group with urticaria a subgroup of cases with selective intolerance to a single NSAID has been reported.² Thus a protocol was carried out to define properly these subgroups and separate the cases with intolerance to a single drug from those with intolerance to the whole group. Of the 122 cases initially evaluated, only 43 proved to be positive when challenged. Eighteen of these responded to several NSAIDs (41%) (group A), and 25 responded to only one drug (58%) (group B). In group A all the patients had urticaria and/or angioedema, but in group B anaphylaxis was reported in 11 cases. Similar data to our results have been reported previously.² Although the commonly proposed mechanism for the reaction in group A is due to interference with prostaglandin synthesis, in group B it is still unknown, although in some cases an IgE-mediated reaction has been reported.^{21,22} Five cases of the 18 in group A had a positive response to piroxicam, whereas all the cases in group B tolerated piroxicam. The property of piroxicam for inhibiting prostaglandin synthesis seems to be the common mechanism for the cross-reactivity with the other NSAIDs. According to the results of our study, piroxicam seems to be less potent than ASA and indomethacin, which indicates that this drug is better tolerated. The inhibition of the cyclooxygenase pathway with a shunting of the arachidonic acid substrate for an increase in the synthesis of 5-lipoxygenase products has been proposed as a cause,^{3,11} although further experimental support is lacking.²³ Piroxicam is an acid with a planar aromatic ring system similar to other NSAIDs but without the carboxylic moiety.⁸ Whether differences in the tolerability are related to differences of the structure are at present unknown. Further studies are required to elucidate this question.

In summary, piroxicam has the potential capacity for inducing a positive response in patients with intolerance to NSAIDs. In 27% of the group of patients

studied, a positive response appeared, indicating that this drug must be administered with caution to patients with intolerance to these drugs. Studies to determine the cross-reactivity of this drug in a group with asthma and intolerance to NSAIDs are at present in progress.

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