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TITLE: IMMEDIATE HYPERSENSITIVITY REACTIONS TO IBUPROFEN AND OTHER ARYLPROPIONIC ACID DERIVATIVES

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ABSTRACT

Background: Although ibuprofen and other arylpropionic acid derivatives (APs) are the most common medicines involved in hypersensitivity drug reactions (HDRs) to NSAIDs, no patient series studies have been performed regarding immediate selective reactions (SRs) to these drugs.

Objective: To characterise patients with immediate selective HDRs to ibuprofen and other APs through clinical history and challenge.

Methods: Subjects who developed an HDR to APs less than one hour after drug intake were included. Tolerance to aspirin was assessed and challenge was performed with ibuprofen in all cases, and additionally with the culprit drug (if different) in those patients that tolerated ibuprofen. Serum tryptase levels and tryptase immunohistochemical staining in skin biopsies were also assessed in some patients with a positive DPT to ibuprofen.

Results: From a total of 245 patients with a confirmed history of HDRs to APs, 17% were classified as selective immediate hypersensitivity reactors by both clinical history and challenge. A selective response to naproxen and dexketoprofen with tolerance to ibuprofen was found in 16 out of 20 cases. Significant differences in serum tryptase levels were observed between 2 and 24 hours in the 11 cases that were studied further.

Conclusions: Within the group of patients with HDRs to NSAIDs, APs can induce immediate SRs. Within this group, selective responses to a single drug or responders to several APs may exist, suggesting potential immunological cross-reactivity.

ABBREVIATIONS:

APs: arylpropionic acid derivatives

ASA: aspirin

CI: cross-intolerance

COX-1: cyclooxygenase-1

DPT: drug provocation test

HDRs: hypersensitivity drug reactions

NSAIDs: non-steroidal anti-inflammatory drugs

SRs: selective reactions

INTRODUCTION

Non-steroidal anti-inflammatory drugs (NSAIDs) are the most commonly used drugs and widely prescribed for treating pain and inflammatory conditions (1-3). However they also induce a number of adverse reactions that can be classified as type A (dose-dependent) or type B (dose-independent) (1-3). The latter includes hypersensitivity drug reactions (HDRs), which are triggered by the release of inflammatory mediators eliciting a variety of clinical entities ranging from urticaria and angioedema to anaphylactic shock and bronchial asthma (4, 5).

Recent data shows that NSAIDs are the most frequent cause of HDRs (2, 5, 6). The underlying mechanism can involve a specific immunological response mediated by IgE antibodies or T cells (selective reactions, SRs) or a non-immunological response related to the inhibition of the cyclooxygenase (COX)-1 enzyme and subsequent release of inflammatory mediators from the arachidonic acid pathway (cross-intolerance, CI) (1, 7-9). Currently, non-immunologically mediated clinical entities are the best studied models (10-12). However, SRs also play a fundamental role in HDRs to NSAIDs, being

the main trigger of drug-induced anaphylaxis (6, 13) and it has recently been reported that in some countries they represent the most frequent type of NSAID-hypersensitivity (14).

Due to its wide use as an antipyretic and analgesic, ibuprofen is the most commonly prescribed arylpropionic acid derivative (AP) at all age ranges, followed by naproxen, dexketoprofen and ketoprofen (15). As strong COX-1 inhibitors, these drugs should not be employed in patients with NSAIDs-exacerbated respiratory disease (NERD), NSAIDs-exacerbated cutaneous disease (NECD) or NSAIDs-induced urticaria/angioedema (NIUA) (7, 10, 11). Concerning SRs, most available information comes from delayed reactions such as photoallergy, fixed drug eruptions, exanthemas, and to a lesser extent from severe reactions like toxic epidermal necrolysis (1, 3, 16). However, immediate SRs, which include anaphylaxis and urticaria/angioedema, are less well studied (8). There is a lack of appropriate *in vitro* and *in vivo* tests to identify these drugs as the culprits and to elucidate the underlying immunological mechanism. Because these drugs can induce anaphylaxis and other severe reactions, diagnosis can only be carried out in centres with specialised resources, expertise and facilities for evaluating these patients (2, 11, 12).

The aim of this work was to study in detail a group of subjects who developed selective reactions such as anaphylaxis and urticaria/angioedema to ibuprofen and/or other APs within the first hour after drug intake. These patients were studied at a clinical centre integrated into the Spanish Network for the Study of Adverse Reactions to Allergens and Drugs (RIRAAF).

METHODS

Patient selection

All cases with a drug reaction suggestive of hypersensitivity to APs recruited in the Infanta Leonor hospital were studied, according to a previously described protocol (4) with some modifications (Figure 1). Those patients with a positive drug provocation test (DPT) to aspirin (ASA) were diagnosed as cross-intolerant and not considered further. All individuals with negative DPT to ASA were challenged with ibuprofen even if this was not the culprit AP. In patients with good tolerance to therapeutic doses of ibuprofen, tolerance or response to the culprit AP (if this was different to ibuprofen) was assessed. In a subgroup of cases where ibuprofen was the culprit drug an alternative AP was also administered to establish cross-reactivity between APs. In this work we present those cases who tolerated ASA and developed an immediate reaction to APs after drug challenge.

This study was performed according to the principles of the Declaration of Helsinki and approved by the local ethics committee. All participants were informed orally about the study and signed the corresponding informed consent.

Drug provocation test

Challenge with ASA

During the first day of DPT with ASA we used 50, 100, and 150 mg at 90 minute intervals (up to a cumulative dose of 300 mg). If the patient did not develop any reaction during the subsequent 48 hours, a week later we administered 150 and 350 mg (cumulative dose 500 mg) at 90 minute intervals. If the patient still did not react after undergoing this procedure for 48 hours, a week later they received 500 mg of ASA every 8 hours for two days. If tolerance was observed throughout, ibuprofen challenge was performed a week later.

Challenge with ibuprofen and other APs

DPT with ibuprofen was performed in all patients by giving incremental doses of 50, 100, 150 and 300 mg every 60 minutes during one day. In those cases who reported severe reactions like anaphylaxis or anaphylactic shock (17) the starting dose was 5 mg but for urticaria and/or angioedema the first dose was 50 mg. In patients for whom the full therapeutic dose could be tolerated, this dose was re-administered after a time interval of a week.

In those cases with a negative DPT to ibuprofen the culprit AP was administered. For naproxen we used doses of 5, 50, 100, 150, and 200 mg, whereas for dexketoprofen doses of 5, 20 and 25 mg were administered. As with ibuprofen, after achieving the maximum dose, this dose was re-administered one week later.

Cases where dexketoprofen or naproxen were the culprits involved were also given ibuprofen as stated above. In this way we assessed cross-reactivity between these drugs.

Tryptase determination in serum and affected skin

Serum tryptase levels were determined by immunoassay (UniCap, Phadia, Uppsala, Sweden) 2 and 24 hours after a positive DPT to ibuprofen as reported (18), and values above 15 µg/l were considered elevated.

Statistical analysis

The chi-squared test was used to analyse differences in nominal variables between groups; the Fisher test was used when there were no criteria for using the chi-square test; the Mann-Whitney test was used for quantitative variables, and the Wilcoxon test was used to analyse related samples. All reported p-values represent two-tailed tests, with values <0.05 considered statistically significant.

RESULTS

A total of 245 individuals with a confirmed diagnosis of HDR to APs were evaluated in the Allergy Service of the Infanta Leonor Hospital (Madrid, Spain) between January 2012 and December 2014. The flow-chart of the different outcomes is shown in Figure 1. In 42 patients (17%) a diagnosis of immediate SR to APs was achieved either because of repetitive episodes or a positive DPT. The allergological work-up consisted of a detailed clinical history, DPT with ibuprofen and other APs. The clinical characteristics of these patients are shown in Table 1. The detailed diagnostic algorithm has been described in the Methods section.

The study group included 30 females and 12 males with no age difference between genders (mean 41.17 ± 14.45 and 42.33 ± 18.71 years respectively, $p=0.829$). Patients reported a total of 91 episodes, with a mean of 2.17 ± 1.82 episodes per patient (Table 1). Twenty-three patients presented only one episode, 5 presented two, 8 presented three and 6 patients more than 3 (Table 1).

Drugs involved

In 34 patients only one drug was involved in the reaction (80.9%), ibuprofen being the culprit in 14 cases (41.2%), followed by naproxen and dexketoprofen. In 3 patients two drugs were reported to be implicated, being ibuprofen and dexketoprofen in patients No. 23 and 34, and ibuprofen and dipyrrone in patient No. 37 (Table 1). In addition to ibuprofen a reaction was reported for three cases when the patient was taking ibuprofen and dipyrrone simultaneously (cases No. 4, 9 and 27). Patient No. 1 showed two episodes to ibuprofen, and one episode when taking naproxen and diclofenac simultaneously.

Clinical entities

Urticaria/angioedema was the clinical entity in 23 patients (54.8%), whereas anaphylaxis/anaphylactic shock was reported in 12 cases (28.5%), and isolated angioedema in 7 (16.7%) (Table 1). A total of 17 patients developed urticaria and/or angioedema less than 30 minutes after drug intake and 13 between 30-60 minutes (56.7% and 43.3%, respectively; $p=0.537$) (Table 1). Anaphylaxis appeared during the first 30 minutes in 11 patients, whereas for patient No. 36 anaphylaxis was reported between 30-60 minutes (Table 1).

When we analysed the differences between the culprit drugs in producing these entities we found that ibuprofen was more likely to induce urticaria/angioedema, whereas naproxen and dexketoprofen induced both anaphylaxis and urticaria/angioedema ($p=0.003$).

Drug provocation test

As stated in the Methods section, tolerance to ASA was a prerequisite for classifying these cases as selective. Therefore ASA was first given to all patients considered in this study, including those who reported good tolerance in their clinical history. When, in addition to an AP, another NSAID was taken simultaneously, DPT with this drug was also performed. Tolerance to dipyron was verified in patients No. 4, 9 27, 37 and 40. Similarly, in case No. 1 tolerance to diclofenac was also found.

DPT with ibuprofen was performed in all patients even if this drug was not the culprit (Table 2). In those cases who presented symptoms with ibuprofen (Table 1), the response induced after DPT was similar in its clinical manifestations to those reported by the patients, although of lower intensity. Of these patients, six developed a positive DPT to ibuprofen in less than 30 minutes and 20 in 30-60 minutes (Table 2). The

average cumulative dose for the first group was 169.17 ± 238.69 mg; for the second it was 412.50 ± 225.88 mg ($p=0.031$).

Of the 20 patients whose reactions were not induced by ibuprofen, 16 showed good tolerance to this drug. Therefore in these patients no cross-reactivity was observed between either naproxen or dexketoprofen and ibuprofen. Four cases developed a reaction with ibuprofen and were therefore considered cross-reactive. Patient No. 6, who previously reported anaphylaxis after naproxen intake, developed generalized cutaneous pruritus and wheals, and palpebral angioedema after ibuprofen administration. Patients No. 24, 25 and 38 reported reactions to dexketoprofen developed systemic pruritus and facial wheals with lips angioedema, and cutaneous pruritus and wheals in thorax, respectively (Table 2).

In those cases with confirmed tolerance to ibuprofen, DPT was also performed with the culprit drug (11 with naproxen and 5 with dexketoprofen) (Table 3). A total of 9 patients presented clinical symptoms in less than 30 minutes. The lowest cumulative doses triggering clinical symptoms were generally found in patients who had previously reported anaphylaxis, rather than urticaria, although differences were not statistically significant ($p=0.324$)(Table 3). Hypotension or cardiovascular symptoms did not appear in any of the cases included, and dyspnoea only occurred in two cases, in addition to skin manifestations. Five of the seven patients who reacted after 30-60 minutes developed clinical symptoms compatible with those reported in their clinical history (Table 3). The cumulative dose for the first group was 78.89 ± 59.25 mg, and for the second was 244.28 ± 210.78 mg ($p=0.04$).

Tryptase determination

Serum tryptase levels were determined for 11 cases, at intervals of 2 and 24 hours after symptom appearance, following a positive ibuprofen challenge (Table 4). There was a overall statistically significant decrease in tryptase levels between these time intervals ($p=0.041$). When we compared the reaction reported in the clinical history with the results of DPT challenge and tryptase levels, we found that for several cases with severe reactions (Patients No. 1, 38 and 42), a greater decrease in tryptase was observed, however there were other cases with anaphylaxis in which this did not occur.

DISCUSSION

The relative frequency of SRs *versus* CI appears to differ between countries. In fact, it has been published that SRs represent around 20% of reactions in Spain (4), 34% in Australia (19) and more than 50% in Turkey (14). Some of these differences may be due to pyrazolones consumption, combined with a genetic disposition (4, 14) (20). Other drugs involved in selective reactions include arylacetic derivatives such as diclofenac (21) although specific IgE antibodies have not been found so far (22). Although less is known about hypersensitivity reactions to APs, (the most highly consumed NSAIDs worldwide), it has been suggested that they are the main cause of SRs (19). Although we have previously reported that APs also contribute to SRs (4), a substantial proportion of cases were diagnosed on the basis of repeated episodes to these drugs in individuals with good tolerance to ASA. In other studies reporting ibuprofen-induced anaphylaxis, tolerance to ASA was not verified (23) or the reaction belonged to another category (24).

The aim of this work was to characterise patients with an unequivocal clinical history of an immediate hypersensitivity reaction after APs intake that was also confirmed by challenge.

The clinical characteristics of the patients showed that urticaria was more common than anaphylaxis, as reported by others (19) and that in most instances it appeared associated with angioedema. It could appear at any time interval, in contrast most cases of anaphylaxis occurred after less than 30 minutes, as happens in betalactam-induced anaphylaxis (25). Although we do not know if selective urticarial or anaphylactic responses in this study depend on an IgE mechanism, it is even more difficult to speculate on the underlying mechanisms in those that developed angioedema (26, 27).

When we compared the clinical entities reported by patients and the symptoms elicited after challenge we noted that cases reporting anaphylaxis showed more severe symptoms after challenge and also tended to react to a lower dose although there were no differences concerning time intervals. This is a typical characteristic of IgE-dependent reactions to drugs. For example, anaphylactic reactions have been reported with very low doses of amoxicillin including trace amounts (28), metamizole (29), diclofenac (30) and other drugs (31). When we examined the cumulative dose of ibuprofen needed to provoke a positive DPT (Table 2) we found it was lower in those patients who reacted in less than 30 minutes. Although a similar trend was observed after naproxen and dexketoprofen DPT, these differences were not significant, probably as a consequence of the limited number of cases. Factors affecting AP metabolism and bioavailability can influence the generation of potential haptens and affect protein binding, leading to a hypersensitivity reaction. These include individual enzymatic

polymorphisms (32), gender (33, 34), age (35, 36), and different underlying inflammatory conditions (37, 38).

The purpose of ibuprofen DPT was two-fold. The first was to confirm the immediate selective response, and the second to verify cross-reactivity in those patients where APs other than ibuprofen were the culprits. We assume that in patients who reported immediate hypersensitivity reactions to naproxen or dexketoprofen, positivity to ibuprofen was due to cross-reactivity. Data from this study show that 38% of cases were selective responders to either naproxen or dexketoprofen since they have good tolerance to ibuprofen. However, we did not determine how many patients responding to ibuprofen tolerated other drugs, since the purpose of this work was to establish the existence of patients who developed reactions to naproxen or dexketoprofen but could tolerate ibuprofen.

The mechanism for these reactions is currently not known but we believe it may be IgE-mediated. Oxidative metabolism is the major route for drug biotransformation in APs. This process can generate chemical intermediates capable of reacting with proteins and forming stable drug-protein adducts. Most studies have looked at this process in the context of photoallergic responses (16, 39, 40). Photobinding of APs to human serum albumin has been reported (41) and relevant epitopes in drug-protein photoantigens have been identified (42), as has the participation of drug-specific antibodies (43-45). However, the structures of the antigenic determinants in IgE-mediated reactions to APs are not known. Whether patients with SRs to naproxen or dexketoprofen but good tolerance to ibuprofen can safely take this drug over time is still unclear. The possibility that such subjects recognize specific determinants not present in ibuprofen should be considered. A similar process occurs in patients with selective responses to amoxicillin,

where minor structural differences are responsible for inducing these reactions whereas benzylpenicillin and other betalactams are well tolerated (46).

Although most tryptase levels were within the normal range, changes between the values obtained 2 and 24 hours (following DPT) were statistically significant; however there was not a correspondence with the severity of the reaction. A similar pattern has been observed in other drug hypersensitivity patients (18), however, increased tryptase levels are not always observed in patients with acute allergic reactions (47) and tryptase levels cannot be considered as a definitive marker for an allergic reaction (48). Moreover, in our study challenge was stopped at the first sign of a positive response, therefore the intensity of the stimulus triggering the reaction was lower than the full therapeutic dose, which could also explain why serum tryptase was not elevated.

This work has some limitations. We have only studied cases with reactions appearing within the first hour, not considering patients who react within 1 to 6 hours, who can also be selective reactors. In addition, classification of time intervals according to patient reports may be inaccurate, although good correspondence was found between DPT reaction time and clinical entity, with patients who reported anaphylaxis normally reacting within 30 minutes. Considering cross-reactivity, this was only assessed in cases reacting to naproxen or desketoprofen, however we do not know how many cases originally reacting to ibuprofen may tolerate the other APs. Further studies are in progress concerning this issue.

Summarising, we conclude that APs may induce selective immediate hypersensitivity reactions in patients with good tolerance to ASA. From the total number of cases evaluated, we reported those for whom we could complete the allergological work-up. Since a substantial number of patients with HDRs to APs

responded only to these drugs, they clearly contribute to an important proportion of SRs to NSAIDs. Studies are needed to identify the adducts potentially involved in these reactions and their recognition by IgE antibodies.

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CONFLICT OF INTEREST

The authors declare the do not have any conflict of interest.

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Table 1. Clinical and demographic data for patients included in this study.

Pat No.	Sex	Age	No. of episodes	Culprit drug	Time interval (min)	Reaction
1	F	36	3	Ibuprofen (2), naproxen+diclofenac (1)	<30	Anaphylactic shock
2	F	71	3	Dexketoprofen	<30	Urticaria
3	M	20	1	Ibuprofen	30-60	Angioedema
4	F	31	4	Ibuprofen (3), ibuprofen+dipyrone (1)	<30	Urticaria
5	F	34	3	Ibuprofen	30-60	Urticaria
6	M	36	2	Naproxen	<30	Anaphylaxis
7	F	37	1	Naproxen	30-60	Urticaria
8	F	20	1	Ibuprofen	<30	Urticaria
9	M	26	3	Ibuprofen (2), ibuprofen+dipyrone (1)	<30	Urticaria
10	F	44	2	Naproxen	30-60	Urticaria/angioedema
11	F	33	1	Dexketoprofen	<30	Anaphylactic shock
12	M	35	2	Naproxen	<30	Anaphylaxis
13	F	29	5	Ibuprofen	<30	Urticaria
14	F	61	1	Ibuprofen	30-60	Angioedema
15	M	54	1	Dexketoprofen	<30	Urticaria
16	F	36	1	Dexketoprofen	<30	Anaphylaxis
17	M	68	1	Naproxen	<30	Anaphylaxis
18	F	31	5	Naproxen	<30	Urticaria
19	M	64	1	Ibuprofen	30-60	Angioedema
20	F	61	1	Naproxen	<30	Urticaria/angioedema
21	F	40	1	Naproxen	30-60	Urticaria
22	F	18	1	Ibuprofen	<30	Urticaria
23	F	28	2	Ibuprofen, dexketoprofen	<30	Angioedema
24	F	51	1	Dexketoprofen	<30	Anaphylaxis
25	F	69	3	Dexketoprofen	<30	Urticaria
26	M	56	1	Dexketoprofen	<30	Urticaria
27	M	28	6	Ibuprofen (5), ibuprofen+dipyrone (1)	<30	Angioedema
28	F	22	3	Ibuprofen	<30	Urticaria
29	F	33	3	Ibuprofen	30-60	Urticaria
30	F	45	1	Naproxen	<30	Anaphylaxis
31	M	70	1	Naproxen	<30	Anaphylaxis
32	F	37	1	Ibuprofen	30-60	Urticaria
33	F	62	1	Ibuprofen	<30	Urticaria/angioedema
34	F	26	2	Ibuprofen, dexketoprofen	<30	Angioedema
35	M	24	1	Ibuprofen	30-60	Angioedema
36	F	47	1	Naproxen	30-60	Anaphylaxis
37	M	27	3	Ibuprofen (2), dipyrone (1)	<30	Urticaria
38	F	50	1	Dexketoprofen	<30	Anaphylaxis
39	F	28	1	Ibuprofen	30-60	Urticaria
40	F	54	10	Ibuprofen, dexketoprofen, ibuprofen+dipyrone (1)	30-60	Urticaria
41	F	46	1	Naproxen	<30	Anaphylaxis
42	F	55	4	Ibuprofen	30-60	Urticaria

Table 2. Drug provocation test with ibuprofen.

Patient No.	DPT time interval (min)	Last dose (mg)	Cumulative dose (mg)	Clinical symptoms during ibuprofen DPT
1	10	50	55	Generalized cutaneous pruritus, wheals and dyspnea, and tachycardia
2	NA	300	600	Good tolerance
3	60	150	300	Palpebral angioedema
4	45	300	600	Generalized cutaneous pruritus and wheals
5	15	50	50	Generalized cutaneous pruritus and wheals in arms
6	20	300	650	Generalized cutaneous pruritus and wheals, and palpebral angioedema
7	NA	300	600	Good tolerance
8	45	100	150	Pruritus and facial wheals
9	50	300	600	Cutaneous pruritus and wheals in abdomen and legs
10	NA	300	600	Good tolerance
11	NA	300	650	Good tolerance
12	NA	300	650	Good tolerance
13	30	300	600	Generalized cutaneous pruritus and wheals
14	50	300	600	Palpebral angioedema
15	NA	300	600	Good tolerance
16	NA	300	600	Good tolerance
17	NA	300	650	Good tolerance
18	NA	300	600	Good tolerance
19	55	300	600	Lips angioedema
20	NA	300	600	Good tolerance
21	NA	300	600	Good tolerance
22	60	100	150	Pruritus and wheals localized in face
23	55	300	600	Facial angioedema
24	15	50	55	Systemic pruritus and facial wheals with lips angioedema
25	25	100	150	Cutaneous pruritus and wheals in thorax
26	NA	300	600	Good tolerance
27	45	300	600	Facial angioedema
28	50	300	600	Generalized cutaneous pruritus and wheals
29	30	50	50	Generalized cutaneous pruritus and wheals
30	NA	300	650	Good tolerance
31	NA	300	650	Good tolerance
32	40	50	50	Generalized cutaneous pruritus and wheals
33	30	300	600	Wheals with facial angioedema
34	45	300	600	Facial angioedema
35	50	150	300	Palpebral angioedema
36	NA	300	650	Good tolerance
37	60	300	600	Cutaneous pruritus and wheals in abdomen
38	20	50	55	Generalized pruritus and facial wheals with lips angioedema
39	50	50	50	Generalized cutaneous pruritus and wheals
40	45	150	300	Generalized cutaneous pruritus and wheals
41	NA	300	650	Good tolerance
42	60	150	300	Generalized cutaneous pruritus and wheals

Table 3. Drug provocation test with arylpropionics other than ibuprofen.

Patient No.	Drug used in DPT	DPT time interval (min)	Last dose (mg)	Cumulative dose (mg)	Clinical symptoms during DPT with the culprit
2	Dexketoprofen	25	20	50	Pruritus and wheals in abdomen
7	Naproxen	40	150	300	Pruritus and wheals in thorax
10	Naproxen	55	150	300	Generalized cutaneous pruritus and lips angioedema
11	Dexketoprofen	15	10	15	Generalized pruritus and throat tightness
12	Naproxen	20	50	55	Generalized cutaneous pruritus and wheals with angioedema
15	Dexketoprofen	30	15	30	Cutaneous pruritus and wheals in abdomen
16	Dexketoprofen	15	10	15	Generalized cutaneous pruritus with wheals and throat tightness
17	Naproxen	20	100	155	Palmoplantar pruritus and wheals in legs
18	Naproxen	40	50	50	Cutaneous pruritus and wheals in thorax, abdomen and legs
20	Naproxen	60	200	500	Generalized cutaneous pruritus and wheals
21	Naproxen	50	200	500	Pruritus and wheals in thorax
26	Dexketoprofen	40	15	30	Generalized pruritus and wheals in arms
30	Naproxen	15	100	155	Generalized cutaneous pruritus and wheals, throat tightness and dyspnea
31	Naproxen	20	50	55	Palmoplantar followed by generalized cutaneous pruritus and wheals
36	Naproxen	20	50	55	Palmoplantar pruritus, urticaria and oedema
41	Naproxen	15	100	155	Generalized pruritus and wheals, throat tightness and dyspnea

Table 4. Correspondence between the clinical patterns according to the clinical history, manifestations during DPT and serum tryptase levels.

Patient No.	Reaction (clinical history)	Cumulative dose (mg)	Clinical symptoms during ibuprofen DPT	Tryptase 2h (µg/l)	Tryptase 24 h (µg/l)
1	Anaphylaxis	55	Generalized cutaneous pruritus, wheals and dyspnea, and tachycardia	10,75	4,55
3	Angioedema	300	Palpebral angioedema	3,75	4,35
5	Urticaria	50	Generalized cutaneous pruritus and wheals in arms	4,25	3,45
6	Anaphylaxis	650	Generalized cutaneous pruritus and wheals, and palpebral angioedema	8,55	6,75
8	Urticaria	150	Pruritus and facial wheals	7,45	6,25
9	Urticaria	600	Cutaneous pruritus and wheals in abdomen and legs	5,75	4,75
22	Urticaria	150	Pruritus and wheals localized in face	7,25	8,1
24	Anaphylaxis	55	Systemic pruritus and facial wheals with lips angioedema	5,25	4,3
28	Urticaria	600	Generalized cutaneous pruritus and wheals	4,25	5,25
38	Anaphylaxis	55	Generalized pruritus and facial wheals with lips angioedema	9,25	4,23
42	Urticaria	300	Generalized cutaneous pruritus and wheals	9,45	6,25

FIGURE LEGENDS

Figure 1. Algorithm for the allergological work-up.

