IMMEDIATE REACTIONS TO MORE THAN ONE NSAID MUST NOT BE CONSIDERED AS CROSS-HYPERSENSITIVITY UNLESS ASA TOLERANCE IS VERIFIED

Brief running title: Multiple NSAIDs immediate reactions

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ABSTRACT

Background: Subjects who develop drug hypersensitivity reactions (DHRs) to chemically unrelated non-steroidal anti-inflammatory drugs (NSAIDs) are considered cross-hypersensitive. The hallmark for this category is that they present a reaction after ASA intake or challenge. Whether patients react to two or more NSAIDs with tolerance to ASA remains to be studied (selective reactions, SRs).

Objective: To identify patients with SRs to two or more NSAIDs including strong COX-1 inhibitors.

Methods: Patients who attended to the Infanta Leonor allergy service with DHRs to NSAIDs were evaluated from January 2011 to December 2014. Those with two or more immediate reactions occurring in less than one hour after drug intake were considered. After confirming ASA tolerance, the selectivity of the response to two or more NSAIDs was demonstrated either by in vivo and/or in vitro testing or by controlled administration.

Results: From a total of 203 patients with immediate DHRs to NSAIDs 16 (7.9%) met the criteria required. They presented a total of 68 anaphylactic or cutaneous reactions (mean of 4.2±2.1). The highest number of reactions appeared to ibuprofen and other arylpropionic acid derivatives, and to metamizole. Two different NSAIDs were involved for 11 patients and three for 5.

Conclusions: Subjects with anaphylaxis or urticaria/angioedema to different NSAIDs should not be considered cross-hypersensitive unless ASA tolerance is verified.

KEYWORDS: NSAID-hypersensitivity, immediate reactions, cross-hypersensitivity, selective reactions.

RESUMEN

Introducción: Los individuos que desarrollan reacciones de hipersensibilidad a antiinflamatorios no esteroideos (AINES) no relacionados químicamente se consideran intolerantes cruzados. La característica esencial para ser incluidos en esta categoría es que presenten un resultado positivo tras la administración de AAS. La cuestión de si estos pacientes responden a dos o más AINES y toleran AAS no ha sido estudiada (reacciones selectivas a múltiples AINES, RS).

Objetivos: Identificar pacientes con RS a dos o más AINES, incluidos inhibidores potentes de COX-1.

Métodos: Se evaluaron los pacientes que acudieron al servicio de alergia del Hospital Infanta Leonor con una historia de hipersensibilidad a AINES desde enero de 2011 a diciembre de 2014. Únicamente se consideraron los casos con dos o más reacciones a AINES diferentes y que se produjeron durante la primera hora tras la ingesta del fármaco (reacciones inmediatas). Tras confirmar la tolerancia a AAS, se evaluó la selectividad de la reacción mediante pruebas *in vivo*/*in vitro* o administración controlada del medicamento.

Resultados: De un total de 203 pacientes con reacciones inmediatas a AINES 16 (7.9%) se ajustaron a los criterios establecidos. Los pacientes presentaron 68 reacciones anafilácticas o urticaria/angioedema (media de 4.2±2.1). El ibuprofeno y otros derivados arilpropiónicos y el metamizol fueron los fármacos más frecuentemente implicados. En 11 pacientes las reacciones fueron inducidas por dos AINES diferentes, mientras que en otros 5 fueron tres los medicamentos implicados.

Conclusiones: Los pacientes con anafilaxia o urticaria/angioedema a diferentes AINES no deben ser incluidos dentro del grupo de intolerancia cruzada hasta verificar su tolerancia a AAS.

PALABRAS CLAVE: Hipersensibilidad a AINES, reacciones inmediatas, hipersensibilidad cruzada, reacciones selectivas.

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STATEMENT OF CONFLICT OF INTEREST

All the authors have no conflicts of interest to declare. All authors have read and approved the manuscript.

INTRODUCTION

Non-steroidal anti-inflammatory drugs (NSAIDs) are the most frequent triggers of drug hypersensitivity reactions (DHRs) [1]. In recent years a number of studies have supported these findings [2-5]. In contrast to reactions to betalactams (BLs), that are immunologically-mediated [6], DHRs to NSAIDs may be induced by both specific immunological mechanisms (allergic or selective reactions, SRs) and without immunological recognition (cross-hypersensitivity, CRs) [7]. Although the latter is responsible for the largest number of affected patients in some countries [1, 8], SRs represent an important proportion in others [9, 10]. SRs have been reported to all NSAIDs independently of their capacity for inhibiting the COX-1 enzyme [9, 11], and in all age ranges including children [12, 13]. Subjects with CRs to NSAIDs react to strong COX-1 inhibitors, including ASA [7]. In fact, ASA administration is required for discriminating between SRs and CRs [7, 14].

DHRs are becoming a problem of great concern [15, 16], with an increase in the number of drugs and mechanisms involved [1]. The two major culprit groups involved in DHRs in both children and adults are NSAIDs and BLs [1, 2]. In fact, hypersensitivity to one drug is considered a risk factor for developing reactions to others [17, 18].

The first evidence of reactions to several drugs in one individual was provided by Harris [19] and later by Sullivan [20] and referred to antibiotics. This condition was originally deemed multidrug allergy syndrome. However, this denomination was based on general assumptions without reference to the potential underling mechanisms [21, 22]. When a specific immunological mechanism is involved, for example in immediate reactions to BLs, the coexistence of IgE antibodies has not been so far proved [23], with the exception of anaphylactic reactions to amoxicillin-clavulanic acid where clinical observations indicate that subjects can have an immediate reaction to both drugs [18]. Concerning T cell responses to drugs a number of studies have shown that non-immediate reactions can occur with different chemically unrelated drugs [24, 25].

Regarding DHRs to NSAIDs, a major question is the existence of SRs to unrelated NSAIDs. There is some evidence indicating that subjects may react to several NSAIDs but tolerate ASA [10, 26]. Contrary to BL reactions, where all drugs share a common ring that may influence the specificity of the response and cross-reactivity [6, 18], NSAIDs comprise a heterogeneous family of chemical structures with a variable

degree of cross-reactivity within each group [9, 11]. In this manuscript we present a series of patients who developed immediate SRs to two or more NSAIDs, and verify tolerance to ASA as well as the involvement of the culprit drug(s) by challenge.

METHODS

Patient selection

Patients who attended to the Allergy Service of the Infanta Leonor Hospital after suffering DHRs attributed to NSAIDs from January 2011 to December 2014 were evaluated. Those patients with challenge-confirmed DHRs to two or more chemically unrelated NSAIDs and tolerance to ASA were considered to have SRs to several NSAIDs and included in this study.

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.

Allergological work-up

The general diagnostic algorithm is outlined in Figure 1. Skin testing was performed with those drugs where evidence for positive immediate results already existed: metamizole [27], paracetamol [28] and diclofenac [29]. Concentrations were used as previously reported [29-31]. Basophil activation test (BAT) was performed exclusively for pyrazolones derivatives as described [27].

For drug challenge we used previously described concentrations [8]. In those patients who presented more than 2 episodes with the same drug, challenge with the culprit was not performed.

Statistical analysis

The chi-squared test was used to analyse differences in nominal variables between groups and the Mann–Whitney test was used for quantitative variables. All reported p-values represented two-tailed tests, with values <0.05 considered statistically significant.

RESULTS

Demographic and clinical characteristics

From a total of 697 patients with confirmed diagnosis of NSAID-hypersensitivity 203 presented SRs. Of these, 16 individuals met the inclusion criteria to

be considered selective reactors to several NSAIDs. All patients included in this study did not refer an allergic reaction to BLs, other antibiotics or to other drugs.

Demographic and clinical characteristics of patients are shown in Table I, with no statistically significant differences in age between females and males (47.2±12.8 and 34.8±12.1 years respectively). Females were more commonly affected. A total of 68 episodes were registered in the clinical histories reported (mean of 4.2±2.1), with no sex differences. Two NSAIDs were the culprits in 11 patients whereas in the other 5 three NSAIDs were implicated. The drugs eliciting the episodes were metamizole (27 episodes, 39.7%), ibuprofen (22 episodes, 32.4%), paracetamol (6 episodes, 8.8%), desketoprofen (5 episodes, 7.4%), naproxen (4 episodes, 5.9%), diclofenac (3 episodes, 4.4%) and celecoxib (1 episode, 1.4%) (Table I). When groups of NSAIDs were considered arylpropionic derivatives induced the highest number of episodes (45.6%, $p<0.001$). Focusing on patients, metamizole induced a reaction in 15 of 16 of them, followed by ibuprofen in 8 of 16 cases ($p<0.001$). If we consider the arylpropionic group, this was implicated in 75% of the patients ($p=0.046$). Interestingly, paracetamol also induced DHRs in 3 patients, being responsible for a total of 6 episodes.

According to the clinical history, the time interval between drug intake and the appearance of symptoms was variable. For ibuprofen it was less than 30 minutes in 5 patients and between 30 and 60 minutes in 3 cases. In all patients where several episodes to the same drug occurred the time interval was similar. For naproxen the time interval was less than 30 minutes in all cases. For metamizole the interval was less than 30 minutes for 12 patients and 30-60 minutes for 3. Concerning clinical entities, anaphylactic shock occurred in 6 patients, anaphylaxis in 6, urticaria in 9, and urticaria/angioedema in 3. Isolated angioedema only appeared in one subject (Table I).

When focusing on the number of episodes per patient, one patient had 10 episodes, 3 reported 6, 2 had 5, 4 had 4, 2 had 3 and 4 had 2 (Table I). This indicated that 75% of cases had three or more episodes. When repeated clinical entities occurred with the same drug these tended to appear with the same time interval and presented with similar clinical characteristics.

Allergological work-up

Data from patients with reactions to metamizole are shown in Table II. Seven out of 15 patients showed a positive skin test result (2 by prick and 5 by intradermal tests). In the remaining 8 cases with a negative skin test, BAT was performed, giving a

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positive result in 4 patients. Therefore, 11 cases could be diagnosed by in vivo/in vitro testing. In 3 patients diagnosis was achieved by positive challenge (Table II). In patient No. 9, for whom both skin testing and BAT were negative, a challenge was not performed since the patient had previously suffered from 3 repeated episodes of anaphylaxis and had cardiovascular risk factors. According to their clinical history all patients with positive intradermal skin test (patients No. 2, 4, 7, 12 and 15) become negative five years after the last evaluation, and those with positive prick test become negative but intradermal still remained positive. In those patients with negative skin test but positive BAT (patients No 1, 3, 10 and 16), the latter also become negative two years after (see Table II).

The results from the allergological work-up with the other NSAIDs are presented in Table III. For arylpropionic acid derivatives, where skin test and BAT have not been validated, these procedures were not carried out. Challenge was performed in those patients who reported only one or two episodes with the same drug or drug group (patient No. 1, 5, 8, 11, 13, 14 and 16). In those cases where naproxen was involved the cumulative dose was 55 mg in 3 cases and 155 mg in one case. One patient responded to a cumulative dose of 155 mg of ibuprofen and another to 500 mg. Finally, patient No. 16 reacted to a cumulative dose of 50 mg of desketoprofen. All patients who reacted to arylpropionics did so at quantities below therapeutic doses with the exception of patient No. 11.

Diagnosis was also achieved by challenge for the remaining drugs (Table III). In all cases were diclofenac and/or paracetamol were involved, skin test were negative at the maximum concentration recommended. Concerning diclofenac challenge, the cumulative dose eliciting a positive result was 30 mg for patient No. 9 and 15, whereas patient No. 2 developed a reaction after a cumulative dose of 50 mg. In the case of paracetamol the two DPT were positive after respective cumulative doses of 500 mg. Finally, a positive result to celecoxib challenge was obtained with a cumulative dose of 120 mg.

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DISCUSSION

In this study we focused on immediate SRs to different NSAIDs occurring less than one hour after drug intake. According to recent guidelines these fall within the category of *single-NSAID-induced urticaria/angioedema or anaphylaxis*, for which all patients must have tolerance to ASA [7, 30]. From a total of 203 patients with immediate SRs to NSAIDs we identified 16 patients who reacted to two or three chemically unrelated NSAIDs along with ASA tolerance. In contrast to hypersensitivity to BLs [21, 31], patients with DHRs to NSAIDs often suffer from repeated episodes due to the incomplete knowledge for dealing with these reactions [8, 32]. Although multiple allergy to drugs was first reported more than 20 years ago [19, 20], studies trying to understand the mechanism have been carried out only for T cell-dependent reactions where sensitisation to multiple drugs could occur both simultaneously and sequentially [19-21]. An imbalance of the immune system caused by effector and/or regulatory T-cells can be involved [24, 33].

Considering immediate SRs to NSAIDs, some subjects can react to two different NSAIDs whilst tolerating ASA [10]. In this manuscript we have shown a series of cases who after reporting repeated episodes of immediate reactions to two or more different NSAIDs demonstrated tolerance to ASA.

Concerning arylpropionic acid derivatives, current data indicate that they are increasingly involved in immediate SRs, approaching the frequency of pyrazolones derivatives [1, 2, 8]. Although these drugs generate immunogenic adducts and induce T cell responses [34], the potential adducts involved in selective immediate allergic reactions and the presence of specific IgE antibodies has not been yet reported [9].

Other drug of interest was metamizole, a frequent elicitor of SRs [9, 35] in countries where it is still highly prescribed [1, 8, 10]. In our study those patients with positive skin test or BAT results became negative over time, as usually occurs in IgE responses to drugs [27]. The analysis of all cases that developed a response to metamizole showed that 43.75% were skin test positive, a figure similar to those reported (Table 2).

Considering the other drugs where skin tests was performed (diclofenac and paracetamol) we did not find any positive response although some studies have shown this can occur [28]. Therefore in those patients with only one reported episode or negative skin test drug involvement was established by DPT as reported [8]. Our results

showed that most subjects responded at low drug concentrations. This agrees with previous data showing that selective responders reacted at lower concentrations compared to cross-hypersensitive individuals [8].

In all cases studied, reactions appeared less than one hour after drug intake. In cases similar to those described here the presence of IgE antibodies has only been found for pyrazolones and ASA [36, 37]. Although clinical evidence suggests an IgE mechanism for diclofenac, with some cases being skin test positive, the presence of specific IgE antibodies has not been demonstrated [29]. In our study all diclofenac cases were skin test negative, as has been reported by others [38, 39].

An intriguing question is why these patients developed an IgE response to several chemically unrelated NSAIDs but not to other drug such as BLs, the classical drugs involved in IgE-mediated reactions. All patients included in this study reported tolerance to BLs and other antibiotics.

Another question concerns the prevalence of immediate SRs. It could be assumed that reactors to several NSAIDs also react to ASA following published guidelines [7, 14]. However, according to our results subjects responding to different NSAIDs should be tested for ASA tolerance. If consistent histories are provided, especially of repeated episodes to different NSAIDs, and tolerance to ASA is proven, the diagnosis of a SR to several NSAIDs must be considered. Although 7.9% represents the proportion of cases in our series, the exact figure of subjects who may develop immediate SRs to two or more NSAIDs remains to be elucidated. Contributing factors are the number of NSAIDs and the time elapsed before patient evaluation. The larger the number of NSAIDs taken and the longer the time patients are exposed, the higher the probability of developing a new reaction although the influence of genetic background must also be considered.

Summarising, we have shown that immediate SRs to two or more NSAIDs do occur and that this phenotype must be taken into account in those cases who report immediate reactions to different analgesics and NSAIDs, whilst having tolerance to ASA. Further studies are in progress in order to determine the prevalence of such reactions.

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LEGEND TO THE FIGURES

Figure 1. Algorithm for the allergological work-up.

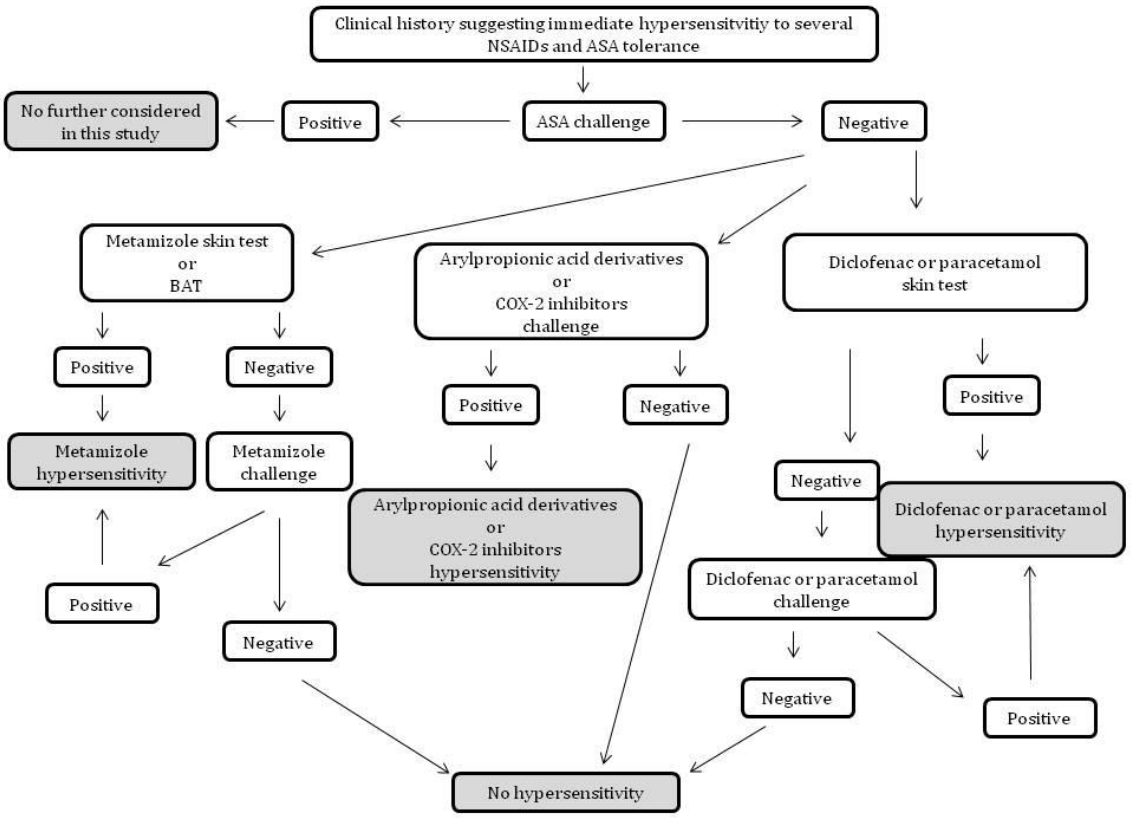

Table 1. Demographic and clinical data of the patients.

Patient No.	Sex	Age (years)	Total of episodes	Drugs involved and episodes (n)	Time interval (min)	Reaction
1	F	51	2	Metamizole (1) Naproxen (1)	< 30 < 30	Anaphylactic shock Anaphylactic shock
2	M	50	3	Metamizole (2) Diclofenac (1)	< 30 < 30	Anaphylactic shock Urticaria/angioedema
3	F	32	4	Ibuprofen (3) Metamizole (1)	< 30 < 30	Urticaria Urticaria
4	F	53	10	Ibuprofen (5) Dexketoprofen (1) Metamizole (4)	30-60 30-60 30-60	Urticaria Urticaria Urticaria
5	F	45	2	Metamizole (1) Naproxen (1)	< 30 < 30	Anaphylactic shock Anaphylaxis
6	M	28	6	Ibuprofen (4) Metamizole (2)	< 30 < 30	Angioedema Angioedema
7	F	43	4	Paracetamol (2) Celecoxib (1) Metamizole (1)	< 30 < 30 30-60	Urticaria/angioedema Urticaria Urticaria
8	M	38	5	Ibuprofen (1) Metamizole (1) Paracetamol (3)	< 30 < 30 < 30	Anaphylaxis Anaphylaxis Urticaria
9	F	72	4	Diclofenac (1) Metamizole (3)	30-60 30-60	Anaphylaxis Anaphylaxis
10	F	23	5	Ibuprofen (1) Dexketoprofen (3) Metamizole (1)	< 30 < 30 < 30	Anaphylaxis Urticaria Anaphylaxis
11	M	18	4	Ibuprofen (2) Metamizole (2)	30-60 < 30	Urticaria/angioedema Urticaria
12	F	42	6	Ibuprofen (4) Metamizole (2)	< 30 < 30	Urticaria Urticaria
13	F	54	2	Paracetamol (1) Naproxen (1)	30-60 < 30	Urticaria Anaphylactic shock
14	F	55	2	Metamizole (1) Naproxen (1)	< 30 < 30	Anaphylactic shock Anaphylaxis
15	M	40	3	Metamizole (2) Diclofenac (1)	< 30 < 30	Anaphylactic shock Urticaria/angioedema
16	F	50	6	Ibuprofen (2) Dexketoprofen (1) Metamizole (3)	30-60 30-60 < 30	Urticaria Urticaria Anaphylaxis

Table 2. Allergological study with metamizole.

Patient No.	Last episode (months)	Skin test	BAT	DPT
1	8	Negative	Positive	ND
2	12	Positive (ID)	ND	ND
3	14	Negative	Positive	ND
4	12	Positive (ID)	ND	ND
5	4	Positive (prick)	ND	ND
6	12	Negative	Negative	Facial and lips angioedema (cumulative dose of 200 mg)
7	8	Positive (ID)	ND	ND
8	10	Negative	Negative	Systemic pruritus, chest and abdominal erythema (cumulative dose of 15 mg)
9	8	ND	Negative	ND
10	12	Negative	Positive	ND
11	18	Negative	Negative	Facial erythema and generalizad pruritus (cumulative dose of 115 mg)
12	16	Positive (ID)	ND	ND
14	2	Positive (prick)	ND	ND
15	12	Positive (ID)	ND	ND
16	6	ND	Positive	ND

Abbreviations: BAT, basophil activation test; DPT, drug provocation test; ID, intradermal test; ND, not done.

Table 3. Drug provocation test with other culprit drugs different from metamizole.

Patient No.	Drug	DPT time interval* (min)	Last dose (mg)	Cumulative dose (mg)	Clinical symptoms during DPT
1	Naproxen	5	50	55	Palmoplantar pruritus and wheals in arms and legs
2	Diclofenac	20	20	50	Generalized pruritus and lips angioedema
3	ND				
4	ND				
5	Naproxen	10	50	55	Generalized pruritus and throat tightness
6	ND				
7	Paracetamol	15	200	500	Generalized pruritus with wheals in face and chest
	Celecoxib	20	60	120	Generalized pruritus and wheals in face
8	Ibuprofen	20	100	155	Palmoplantar pruritus and wheals in abdomen and chest
9	Diclofenac	40	15	30	Cutaneous pruritus and wheals in thorax, abdomen and legs
10	ND				
11	Ibuprofen	50	200	500	Pruritus and wheals in thorax
12	ND				
13	Naproxen	15	100	155	Generalized pruritus and wheals, throat tightness and dyspnea
	Paracetamol	30	200	500	Pruritus and wheals in abdomen
14	Naproxen	20	50	55	Palmoplantar followed by generalized pruritus and wheals
15	Diclofenac	20	15	30	Palmoplantar pruritus, urticaria and lips angioedema
16	Dexketoprofen	15	20	50	Generalized pruritus and wheals in thorax, arms and legs

Abbreviations: DPT, drug provocation test; ND, not done.

* Time elapsed between controlled administration of the drug and the appearance of symptoms.