ORIGINAL ARTICLE

Drug Hypersensitivity Reactions: Response Patterns, Drug Involved, and Temporal Variations in a Large Series of Patients

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■ **Abstract**

Background: Drug hypersensitivity reactions (DHRs) are among the most frequent reasons for consultation in allergy departments, and are becoming more common due to increasing prevalence and case complexity.
Objective: To study the clinical characteristics, drugs involved, diagnostic methods, and temporal variation of DHRs in a large series of patients over a 6-year period.
Methods: We included all patients attending our department between 2005 and 2010. The diagnosis was performed by in vivo and/or in vitro tests (basophil activation test and specific immunoglobulin [Ig] E in serum and drug provocation testing [DPT]) when indicated.
Results: We evaluated 4460 patients who reported 4994 episodes (mean [SD] of 1.13 [0.36] [range, 1-3] episodes per patient). Based on clinical history, 37% of the episodes were attributed to nonsteroidal anti-inflammatory drugs (NSAIDs), 29.4% to ß-lactam antibiotics (BLs), 15% to non-BLs, and 18.4% to other drugs. Analysis of the 1683 patients (37.45%) finally confirmed as allergic showed the most frequent diagnosis to be hypersensitivity to multiple NSAIDs (47.29%), followed by immediate reactions to BLs (18.12%). There was an increase in reactions to non-BLs (from 21.2% to 31.9%; *P*<.03) over the study period, mainly due to an increase in allergy to quinolones (from 0.5% to 6.8%; *P*<.02); 44% of patients were diagnosed by clinical history, 14.6% by skin tests, 10.4% by in vitro tests, and 30.8% by DPT.
Conclusions: NSAIDs were the drugs most frequently involved in DHRs and the most common diagnosis was urticaria/angioedema with cross intolerance. Reactions to emerging drugs such as quinolone derivatives and radiocontrast media are becoming more common.

Key words: Drug hypersensitivity. Nonsteroidal anti-inflammatory drugs. ß-Lactams. Epidemiology. Diagnosis.

■ **Resumen**

Introducción: Las reacciones de hipersensibilidad a fármacos (RHF) son una de las causas de consulta más frecuentes en los servicios de alergología, con un incremento en la demanda debido a una mayor prevalencia y complejidad.
Objetivo: Estudiar las características clínicas, fármacos implicados, métodos empleados para el diagnóstico y su variación a lo largo del tiempo en una serie grande de pacientes con historia de RHF en un periodo de 6 años.
Métodos: Se incluyeron todos los pacientes que consultaron en nuestro servicio por RHF entre 2005 y 2010. El diagnóstico fue realizado mediante pruebas *in vivo* y/o *in vitro* (test de activación de basófilos e IgE específica en suero) y test de provocación (TP) en los casos en que estuviese indicado.
Resultados: Evaluamos 4460 pacientes con un total de 4994 episodios (media de 1.13±0.36 (1-3) episodios por paciente). Basándonos en la historia clínica, el 37% de los episodios fueron atribuidos a AINEs, 29.4% a BLs, 15% a antibióticos no-BL y 18.4% a otros fármacos. El análisis de los 1683 (37.45%) pacientes finalmente confirmados como alérgicos mostró que el diagnóstico más frecuente fue la hipersensibilidad a múltiples AINEs (47.29%), seguido de las reacciones inmediatas a BLs (18.12%). Se detectó un incremento en las reacciones producidas por antibióticos no-BL (de 21.2% a 31.9%; p<0.03), principalmente debido a quinolonas (de 0.5% a 6.8%; p<0.02); 44% fueron diagnosticados por historia clínica, 14.6% por pruebas cutáneas, 10.4% por pruebas *in vitro* test y 30.8% por TP.
Conclusiones: Los AINEs fueron los medicamentos más frecuentemente implicados en las RHF, siendo la urticaria/angioedema con intolerancia cruzada el diagnóstico más frecuente. Fármacos emergentes como quinolonas y contrastes yodados están adquiriendo un creciente protagonismo.

Palabras clave: Hipersensibilidad a fármacos. Antiinflamatorios no esteroideos. Betalactámicos. Epidemiología. Diagnóstico.

Introduction

Drug hypersensitivity reactions (DHRs) are a frequent reason for consultation in allergy departments. They include immunologically mediated reactions, where the mechanisms involved may be either immunoglobulin (Ig)–E mediated or T-cell dependent [1,2], and nonimmunologically mediated reactions, the most frequent of which involve cross intolerance of nonsteroidal anti-inflammatory drugs (NSAIDs) [2-5]. It has been difficult to determine the true prevalence of DHRs because of difficulties concerning a precise definition and identification of reactions, as well as a lack of population studies [6]. Figures reported vary and it has been estimated that DHRs account for 3% to 6% of all hospital admissions and that they occur in 10% to 15% of hospitalized patients [7]. However, several biases exist, such as differences in study populations and diagnostic criteria and methods [2,8-11].

DHRs are associated with a high use of health care services, particularly in adults. Indeed, in Spain drug allergy is the third most common reason for consultation in allergy departments, after rhinitis and bronchial asthma [12]. The diagnosis of DHR is usually based on clinical history, skin testing, and to a lesser extent in vitro testing [11]. Clinical history, however, is often not reliable [13], and reagents used in skin testing and/or in vitro diagnosis are seldom standardized, and even when appropriate, if the reaction occurred a long time previously, sensitivity can be lost or the test can show negative results [14]. Thus drug provocation testing (DPT) often remains the sole alternative [13,15]. However, DPT is cumbersome, often dangerous, and sometimes nondefinitive [9,16]. New diagnostic tools, such as the basophil activation test (BAT) for IgE-dependent reactions [17-21] and lymphocyte stimulation studies [22,23] have been proposed, though they are only available at a few centers. Epidemiological studies of DHRs report varying results because of differences in diagnostic methods [1,11,24,25]. Drug allergy is not a static process; it varies over the years and is related to changes in patterns of drug consumption, the introduction of new drugs and the withdrawal of others, and the establishment of new indications [12,16,26-30].

The aim of this study was to describe the clinical characteristics, drugs involved, and methods used for diagnosing patients from the same referral area consulting with a history of DHR over a period of 6 years in a large population of patients evaluated using the same protocols and diagnostic methods. This represents the largest study to date in terms of number of patients and study period.

Methods

Patients

This study was undertaken among patients with a history suggestive of DHR evaluated for the first time at our allergology department. It was conducted over a period of 6 years (January 2005-December 2010). There were no relevant modifications to the work-up procedure throughout the evaluation period and, in fact, the same approach has been used for the last 12 years in our department, which has conducted intensive clinical and basic laboratory research on drug allergy [31]. The procedure consisted of a detailed clinical history [32], skin tests according to the European Network Drug Allergy (ENDA) guidelines [33] and in vitro tests that included determination of specific IgE in serum and BAT [21,33-35]. Specific IgE was determined in cases of immediate reactions to ß-lactam antibiotics (BLs). BAT was performed in cases of immediate reactions to BLs when the skin test was negative and no specific IgE was detected, as well as in cases where BAT has been shown to be useful and no other methods are available, such as with quinolones or proton pump inhibitors. When skin tests and in vitro tests were negative or not indicated, DPT with the suspect drug was carried out [8,15]. When at least 1 of the in vivo or in vitro tests performed was positive, the patient was considered to have a DHR, and when skin and in vitro tests were negative, DPT was performed and, if negative, the patient was classified as nonallergic. Patients who refused to undergo the study or in whom DPT could not be performed were classified as nonconfirmed. Those who reported severe anaphylaxis or severe reactions (toxic epidermal necrolysis-Stevens-Johnson syndrome, acute generalized exanthematous pustulosis, DRESS [drug reaction with eosinophilia and systemic symptoms], and organ-specific reactions) did not undergo DPT.

Skin Tests

A prick test and intradermal test were carried out as described [16,25] in patients with reactions due to BLs or other soluble drugs where a clear immediate reaction was suspected. These drugs were mainly dipyrone, corticosteroids, and iodinated contrast media. In a few instances, skin testing was also performed for other drug groups, and if no published data were available for testing, the procedure was validated for the purpose as recommended [33]. Skin tests were performed using the dilutions shown in Table 1. An increase in the diameter of the wheal area of greater than 3 mm 20 minutes after testing was considered to represent an immediate positive response [25]. A reading was taken after 48 hours in the case of nonimmediate reactions and after 1 week in the case of corticosteroids [36-38].

To evaluate nonimmediate reactions produced by insoluble drugs, patch tests were used as recommended [36,37]. The drugs included were NSAIDs, clindamycin, benzodiazepines, and anticonvulsants. The tests were performed by mixing powdered drug in petrolatum at a concentration of 5% w/w for the following drugs: naproxen, diclofenac, dipyrone, etofenamate, tetrazepam, diazepam, phenytoin, carbamazepine, and valproic acid. The occlusion time was 48 hours. Erythema with edema, papules, vesicles, or bullae 48 and/or 72 hours after testing was considered positive [33,36].

Determination of Specific IgE in Serum

Specific serum IgE was determined using the radioallergosorbent test (RAST) only for BL determinants, as described elsewhere [16,25]. Benzyl penicillin, ampicillin and amoxicillin were used routinely, as well as cephalosporins or other BLs suspected from the clinical history [25].

Basophil Activation Test

The BAT was performed as previously described [19,33,34]. The concentrations used for the different drugs were chosen based on dose-response curves and cytotoxicity studies. The cells were analyzed on a FACSCalibur flow cytometer (Becton Dickinson) by acquiring at least 1000 basophils per sample. Results were considered positive when the stimulation index (SI), calculated as the ratio between the percentage of degranulated basophils with the different drugs and the negative control, was 2 or more for at least 1 of the dilutions used. Working concentrations for these drugs have been previously described [35] and are shown in Table 1.

Table 1. Concentrations of the Different Drugs Used for Skin Prick Testing (SPT), Intradermal Testing (ID), and Basophil Activation Testing (BAT)

Drug	SPT	ID	BAT
Dipyrone	400 mg/mL	4, 40 mg/mL	0.25, 2.5 mg/mL
PPL	$5 \times 10\text{-}5$ mMol/L	$5 \times 10\text{-}5$ mMol/L	0.005, 0.02 mg/mL
MDM	0.02 mMol/L	$2 \times 10\text{-}2$ mMol/L	0.1, 0.5 mg/mL
Benzylpenicillin	10.000 IU/mL	10.000 IU/mL	0.4, 2 mg/mL
Amoxicillin	20 mg/mL	2, 20 mg/mL	0.25, 1.2 mg/mL
Ampicillin	20 mg/mL	2, 20 mg/mL	0.25, 1.2 mg/mL
Cephalosporins	2 mg/mL	0.2, 2 mg/mL	0.25, 1.2 mg/mL
Ciprofloxacin	Not done	Not done	0.2, 2 mg/mL
Moxifloxacin	Not done	Not done	0.1, 0.2 mg/mL
Levofloxacin	Not done	Not done	2, 4 mg/mL
Hydrocortisone	2, 20 mg/mL	0.2, 2 mg/mL	0.5, 0.1, 0.01 mg/mL
Methylprednisolone	2, 20 mg/mL	0.2, 2 mg/mL	0.5, 0.1, 0.01 mg/mL
Iodixanol	320 mg/mL	3.2 mg/mL	Not done
Iohexol	240 mg/mL	24 mg/mL	Not done
Iobitridol	350 mg/mL	35 mg/mL	Not done
Iomeprol	300 mg/mL	30 mg/mL	Not done

Abbreviations: MDM, minor determinant mixture; PPL, penicilloyl-polylysine.

Drug Provocation Testing

Single-blind placebo-controlled DPT was performed following the ENDA general guidelines [15], with slight modifications in some cases. We administered escalating doses of the drug at intervals of 30 to 90 minutes up to the full therapeutic dose. In patients with reactions induced by NSAIDs, DPT was performed as previously described [30]. If cutaneous and/or respiratory symptoms or changes in vital signs (rhythm alterations, decrease in peak expiratory flow rate, or hypotension) appeared, the procedure was stopped and the symptoms were evaluated and treated. If good tolerance was observed, a therapeutic course of 2 days was started 24 hours afterwards. All drugs were given in opaque capsules prepared by the hospital pharmacy service.

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

Statistical Analysis

Nonnormally distributed quantitative variables were compared using the Mann-Whitney test and qualitative variables using the χ^2 test. All reported P values were based on 2-tailed tests, with values of less than .05 considered significant.

Results

Clinical Characteristics of the Patients

A total of 4460 patients with a clinical history of DHR were evaluated over a 6-year period, with a total number of 4994 episodes and a mean (SD) of 1.13 (0.36) (range, 1-3) episodes per patient; 2880 (64.58%) patients were female and 1580 (35.42%) were male, with a mean (SD) age of 43.71 (15.82) years. Children under the age of 14 years were not included. No differences in age or sex were found over the 6-year period (Table 2). We detected an increase in the number of patients evaluated each year because our allergy department experienced a progressive increase in activity, accepting patients from other centers in the area.

Drugs Involved and Clinical Conditions According to Patient Reports

Analysis of the clinical conditions reported by the patients over the study period showed a significant increase in the percentage of urticaria (from 70.8% to 82.6%, P<.0001) and anaphylaxis (from 7.5% to 10.8%, P<.021) and a decrease in the percentage of angioedema without urticaria (from 5.7% to 3.5%; P<.03) (Table 2). There were no significant changes in any of the other conditions over the study period.

Based on clinical history, 1848 (37%) of the episodes were attributed to NSAIDs, 1471 (29.4%) to BLs, 754 (15%) to non-BLs, and 921 (18.4%) to other drugs. Table 2 shows the analysis of the drugs most frequently involved. In the category of NSAIDs, there was a significant increase in the percentage of reactions induced by acetylsalicylic acid (from 15.5% to 20.5%, P<.014) and a nonsignificant decrease in those induced by dipyrone (from 18.03% to 17.7%). Although ibuprofen was the most frequently recorded NSAID, use did not vary significantly over the 6-year study period.

There was a decrease in the percentage of reactions attributed to BLs in general (from 35.5% to 24.8%; P<.0001). When specific BLs was considered, there was a decrease in the percentage of reactions attributed to penicillin (from 8% to 3.9%; P<.002), amoxicillin (from 12.5% to 8%; P<.017), and cephalosporins (from 2.5% to 1.5%; no statistical difference), and an increase in reactions attributed to amoxicillin-clavulanic acid (from 3.5% to 8.7%; P<.0001).

Table 2. Clinical Characteristics, Type of Reactions and Drugs Involved in Patients Studied for Drug Allergy. Data Obtained From Clinical History

		2005	2006	2007	2008	2009	2010	*P*
Patients evaluated, No.		534	564	718	758	885	1001	
Mean (SD) age, y		44.15 (15.21)	44.06 (14.46)	44.26 (13.12)	43.33 (12.81)	44.55 (14.81)	43.35 (14.76)	NS
Sex, % female		61.96	62.34	60.76	61.76	64.32	66.96	NS
Clinical symptom, No. (%) of patients	Urticaria	397 (70.89)	446 (71.93)	633 (78.34)	611 (76.95)	877 (80.97)	933 (82.63)	.0001
	Angioedema	32 (5.7)	34 (5.48)	47 (5.81)	39 (4.91)	39 (3.6)	40 (3.54)	.033
	Anaphylaxis	42 (7.5)	46 (7.42)	61 (7.54)	64 (8.06)	107 (9.87)	122 (10.8)	.021
	Exanthema	13 (2.32)	16 (2.58)	24 (2.97)	21 (2.64)	20 (1.84)	17 (1.5)	NS
	Others	76 (13.57)	78 (12.58)	43 (5.32)	59 (7.43)	40 (3.69)	13 (1.15)	.0001
Diagnoses/patient, No.		1.03 (0.29)	1.09 (0.39)	1.11 (0.37)	1.04 (0.48)	1.21 (0.54)	1.12 (0.36)	NS
Episodes/year, No.		560	620	808	794	1083	1129	NS
Drug involved, No. (%) of patients	NSAIDs	197 (35.17)	227 (36.61)	304 (37.62)	304 (38.28)	405 (37.39)	411 (36.4)	NS
	ASA	87 (15.53)	86 (13.87)	122 (15.09)	126 (15.86)	197 (18.19)	231 (2.46)	.014
	Ibuprofen	112 (20)	136 (21.93)	185 (22.89)	176 (22.16)	264 (24.37)	300 (26.57)	NS
	Dipyrone	101 (18.03)	112 (18.06)	139 (17.2)	138 (17.38)	195 (18)	199 (17.62)	NS
	Diclofenac	50 (8.92)	55 (8.87)	70 (8.66)	65 (8.18)	87 (8.03)	93 (8.23)	NS
	Paracetamol	33 (5.89)	39 (6.29)	51 (6.31)	47 (5.91)	65 (6)	72 (6.37)	NS
	BLs	199 (35.53)	213 (34.35)	250 (30.94)	237 (29.84)	292 (26.96)	280 (24.8)	.0001
	Penicillin	45 (8.03)	53 (8.54)	52 (6.43)	45 (5.66)	54 (4.98)	45 (3.98)	.002
	Amoxicillin	70 (12.5)	86 (13.87)	80 (9.9)	92 (11.58)	87 (8.03)	91 (8.06)	.017
	AX-clavulanic acid	20 (3.57)	26 (4.19)	52 (6.43)	49 (6.17)	74 (6.83)	99 (8.76)	.0001
	Cephalosporin	14 (2.5)	23 (3.7)	34 (4.20)	22 (2.77)	23 (2.12)	17 (1.5	NS
	Non-BLs	50 (8.92)	56 (9.03)	111 (13.73)	127 (15.99)	206 (19.02)	204 (18.06)	.0001
	Quinolones	10 (1.78)	24 (3.87)	35 (4.33)	39 (4.91)	48 (4.43)	52 (4.6)	0.044
	Macrolides	15 (2.67)	16 (2.58)	31 (3.83)	43 (5.41)	65 (6)	70 (6.2)	.0001
	Sulfonamides	11 (1.96)	7 (1.12)	7 (0.86)	8 (1)	5 (0.46)	6 (.53)	NS
	Other drugs	114 (20.35)	124 (20)	143 (17.69)	126 (15.86)	180 (16.62)	234 (2.72)	NS
	Contrast media	12 (2.14)	12 (1.93)	12 (1.48)	19 (2.39)	29 (2.67)	46 (4.07)	.005
	PPIs	5 (0.89)	7 (1.12)	6 (0.74)	9 (1.13)	12 (1.1)	15 (1.32)	NS

Abbreviations: ASA, acetylsalicylic acid; AX, amoxicillin; BL, ß-beta-lactam antibiotics; NSAIDs, nonsteroidal anti-inflammatory drugs; NS, not significant; PPIs, proton pump inhibitors.

An increase was also observed in reactions produced by non-BLs (from 8.9% to 18%; *P*<.0001), in particular quinolones (from 1.78% to 4.6%; *P*<.044). In the category of other drugs, an increase was also observed in reactions attributed to iodinated contrast media (from 2.1% to 4.07%; *P*<.005).

Diagnosis According to Allergy Work-up

After the allergy work-up, one-third of the cases (37.4%) were confirmed as allergic and 49.2% as nonallergic. In 13.4% of cases, the diagnosis was not confirmed due to contraindications for work-up (pregnancy [n=24], heart and lung disease [n=327], infections [n=101], psychiatric disorders [n=26], or refusal to participate [n=126]). No differences were noted between the patients with confirmed allergic conditions and those who refused to participate in terms of clinical conditions reported or drugs involved.

Analysis of confirmed allergy cases showed an increase in reactions produced by non-BLs (from 1.42% to 4.87%; *P*<.0001) and other drugs (from 3.21% to 5.58%; *P*<.0.005); there were no changes in those induced by NSAIDs (from 20.17% to 20.01%) or by BLs (from 8.03% to 6.99%) (data not shown in tables). This indicates that 1 out of every 5 cases initially reported as allergic to NSAIDs was confirmed, though in the case of BLs this proportion was lower (<1 out of every 10 individuals evaluated).

Results of the specific diagnoses in the group of patients confirmed as allergic are shown in Table 3. Comparison of data from the 6-year study period revealed an increase in DHRs caused by quinolones (from 0.5% to 6.8%; *P*<.02) and iodinated contrast media (from 1.08% to 5.9%; *P*<.001) and a decrease in selective responders to NSAIDs (from 11.4% to 4.9%; *P*<.0001). No significant changes were found for cross intolerance of NSAIDS or reactions to BLs.

Table 3. Confirmed Diagnoses for Whole Group

	Diagnosis	2005 No. (%)	2006 No. (%)	2007 No. (%)	2008 No. (%)	2009 No. (%)	2010 No. (%)	P
NSAIDs	Cross intolerance	92 (50)	99 (48.76)	103 (43.64)	105 (45.25)	192 (47.4)	205 (48.46)	NS
	Selective responders	21 (11.41)	24 (11.82)	45 (19.06)	24 (10.34)	32 (7.9)	21 (4.96)	.0001
BLs	Immediate reactions	39 (21.19)	38 (18.71)	46 (19.49)	41 (17.67)	73 (18.02)	68 (16.07)	NS
	Nonimmediate reactions	6 (3.26)	5 (2.46)	1 (0.42)	5 (2.15)	6 (1.48)	11 (2.6)	NS
Non-BLs	HS to quinolones	1 (0.54)	2 (0.98)	8 (3.38)	10 (4.31)	22 (5.43)	29 (6.85)	.02
	HS to macrolides	2 (1.08)	2 (0.98)	1 (0.42)	1 (0.43)	7 (1.72)	9 (2.12)	NS
	HS to metronidazole	0 (0)	1 (0.49)	2 (0.84)	2 (0.86)	5 (1.23)	8 (1.89)	NS
	HS to clindamycin	1 (0.54)	1 (0.49)	2 (0.84)	1 (0.43)	3 (0.74)	5 (1.18)	NS
	HS to sulfonamides	4 (2.17)	5 (2.46)	5 (2.11)	4 (1.72)	6 (1.48)	4 (0.94)	NS
Other drugs	HS to iodinated contrast media	2 (1.08)	2 (0.98)	3 (1.27)	3 (1.29)	13 (3.2)	25 (5.91)	.001
	HS to heparins	0 (0)	0 (0)	2 (0.84)	1 (0.43)	1 (0.24)	0 (0)	NS
	HS to corticosteroids	3 (1.63)	3 (1.47)	6 (2.54)	7 (3.01)	5 (1.23)	10 (2.36)	NS
	HS to proton pump inhibitors	1 (0.54)	1 (0.49)	1 (0.42)	2 (0.86)	2 (0.49)	4 (0.94)	NS
	HS to muscle relaxants	1 (0.54)	2 (0.98)	2 (0.84)	3 (1.29)	2 (0.49)	4 (0.94)	NS
	HS to other drugs	11 (5.98)	18 (8.87)	9 (3.82)	23 (9.91)	36 (8.89)	20 (4.73)	NS

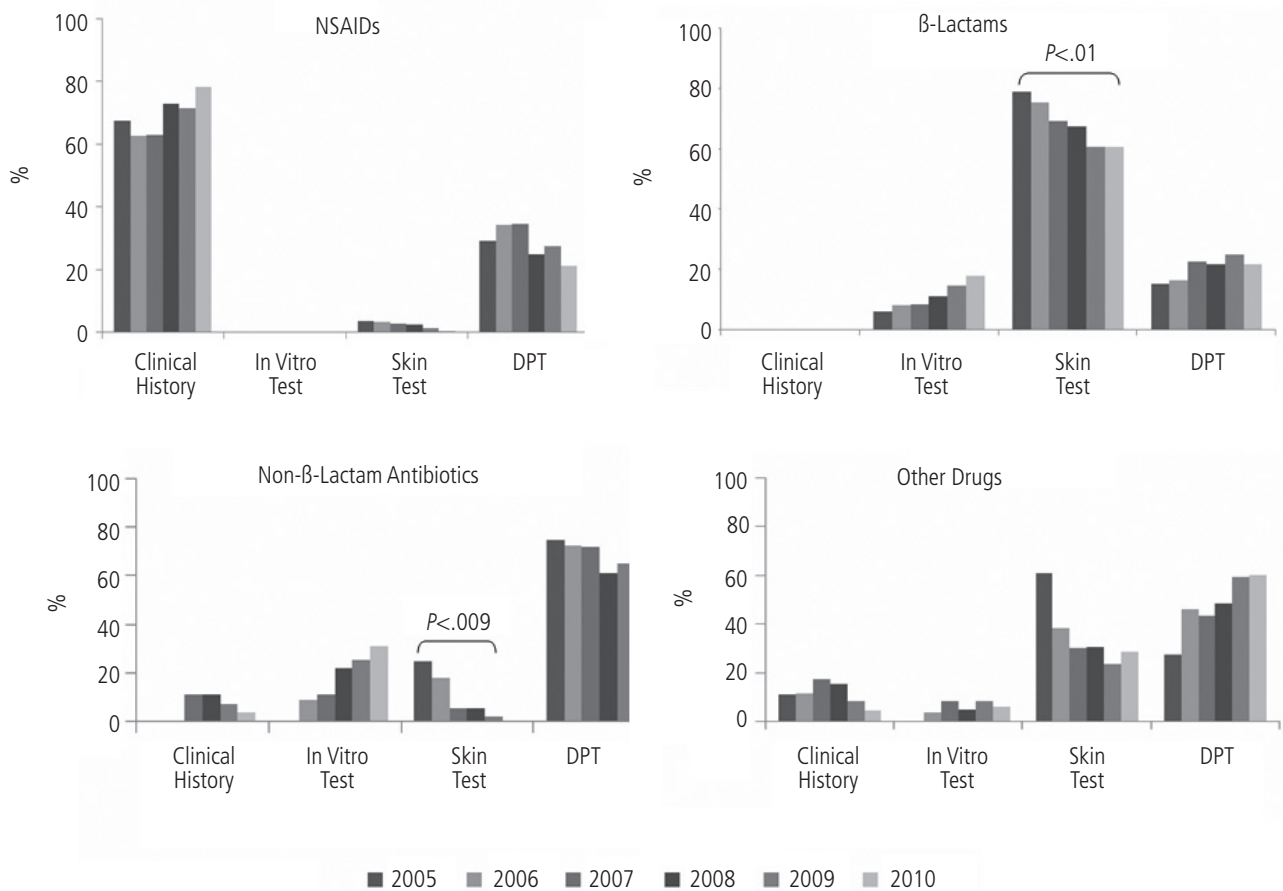Abbreviations: BL, ß-beta-lactam antibiotics; HS, hypersensitivity; NS, not significant.

Figure. Role of different methods (clinical history, in vitro test, skin test, and drug provocation test (DPT) in the diagnosis of drug hypersensitivity. Comparison between groups of drugs (nonsteroidal anti-inflammatory drugs; ß-lactam antibiotics, non-ß-lactam antibiotics, other drugs).

Table 4. Confirmed Diagnosis in Patients With NSAID Hypersensitivity. Comparisons Between Diagnostic Methods

	Diagnosis	2005 No. (%)	2006 No. (%)	2007 No. (%)	2008 No. (%)	2009 No. (%)	2010 No. (%)	P
Clinical history	Cross intolerance	71 (77.17)	73 (73.73)	82 (79.61)	88 (83.8)	153 (79.68)	172 (83.9)	NS
	Selective responders	5 (23.8)	4 (16.66)	11 (24.44)	6 (25)	7 (21.87)	5 (23.8)	NS
Skin test	Cross intolerance	0	0	0	0	0	0	NS
	Selective responders	4 (19.04)	4 (16.66)	4 (8.88)	3 (12.5)	3 (9.37)	1 (4.76)	NS
Drug provocation test	Cross intolerance	21 (22.82)	26 (26.26)	21 (20.38)	17 (16.19)	39 (20.31)	33 (16.09)	NS
	Selective responders	12 (57.14)	16 (66.66)	30 (66.66)	15 (62.5)	22 (68.75)	15 (71.42)	NS

Abbreviations: NS, not significant; NSAID, nonsteroidal anti-inflammatory drugs.

Contribution of Diagnostic Methods

Diagnosis was established by clinical history in 742 patients (44%), by skin tests in 246 patients (14.6%), by in vitro testing in 176 patients (10.4%), and by DPT in 519 patients (30.8%). Thus, DPT was required to establish a diagnosis in almost 1 out of every 3 patients. Comparison over the 6-year study period showed a nonsignificant increase in the percentage of cases diagnosed by clinical history (from 39.8% to 52.5%) and a significant decrease in those diagnosed by skin tests (from 32.86% to 19.48%; $P<.0001$). This was due to the higher number of hypersensitivity reactions to NSAIDs, as detailed below. No significant differences were detected in patients diagnosed by in vitro tests or DPT.

Comparison between drug groups (Figure) showed a decrease in the percentage of patients allergic to NSAIDs who were diagnosed by skin tests (from 3.5% to 0.4%; no significant differences), attributable to a decrease in the percentage of selective responders diagnosed by skin testing (from 19% to 4.7%; no significant differences) (Table 4). No significant differences were detected in those diagnosed by clinical history or DPT.

When this analysis was performed in patients allergic to BLs, we found a nonsignificant increase in the percentage of patients diagnosed by in vitro tests (from 6.1% to 17.8%) and DPT (from 15% to 21.6%) and a significant decrease in those diagnosed by skin tests (from 78.9% to 60.6%; $P<.01$). No patients were diagnosed by clinical history in this group (Figure).

In patients allergic to non-BLs, DPT was the method most frequently used to establish a diagnosis. Comparison over the 6-year study period showed an increase in patients diagnosed by in vitro tests (from 5% to 30.9%; $P<.05$) and a decrease in those diagnosed by skin tests (from 25% to 1%; $P<.009$). This was due to an increase in the number of patients with fluoroquinolone allergy diagnosed by BAT and a decrease in those with sulfonamide allergy diagnosed by skin tests.

In patients who were allergic to other drugs, we detected a decrease in those diagnosed by skin tests (from 61.1% to 28.5%; $P<.05$) and an increase in those diagnosed by DPT

(from 27.7% to 60.3%; $P<.05$) (Figure). This was mainly due to an increase in the percentage of reactions induced by iodinated contrast media.

Discussion

This study evaluated the largest series to date of patients with DHR over a period of 6 consecutive years. Another large series is that of Messaad et al [13], who evaluated 898 patients with a history of immediate drug allergy and performed 1372 challenges over 5 years. Our study also considered delayed-type allergic reactions, which we identified as nonimmediate allergic reactions.

One purpose of this study was to see how many patients claimed to be allergic and how many were actually allergic. Although our center coordinates a national network for drug allergy with a catchment area of more than 8 million individuals, we decided to evaluate and analyze variations over time in a well-controlled population at a single center.

As the study duration was 6 years, we were also able to analyze tendencies in responses and drugs involved. Moreover, analyses of tendencies for single drug groups such as BLs and NSAIDs have already been published [29,30].

We confirmed that women are more likely to develop drug allergies than men. In a study carried out in 2005 in a similar population [12], the female to male ratio of patients with drug allergy was approximately 2:1. Other studies have also shown this predominance [39-42]. Whether this is due to a higher consumption of drugs by women to treat diseases compared with men and/or to other reasons, including genetic predisposition, is not well known [9]. Consumption of NSAIDs, the most frequent group of drugs involved and confirmed as causing allergy, is more common in women than men [43-45]. We detected no significant differences in the age of those with drug allergy and those without, probably because we did not include children in this study.

Excluding NSAIDs, when patients were evaluated before diagnosis, the percentage of clinical conditions indicative

of nonimmediate reactions (probably T-cell mediated) was higher than that indicative of immediate reactions (probably IgE-mediated), with no differences over the 6 years assessed. However, once diagnosis was established, the percentage of immediate reactions was higher than that of nonimmediate reactions and similar over the 6 years. This can be explained by the fact that a high proportion of persons with apparent nonimmediate urticarial and exanthematic reactions are finally diagnosed as having good tolerance of the suspected drugs [40-42]. For NSAIDs, though, the classification between immediate and nonimmediate is not valid because in a high percentage of cases the reaction is caused not by allergy but by cross intolerance [4,5,30].

Concerning IgE-mediated reactions, we observed a significant increase in the percentages of urticaria ($P<.0001$) and anaphylaxis ($P<.021$) due to the involvement of amoxicillin-clavulanic acid and quinolones [46,47]. In fact, we have already reported that clavulanic acid can induce positive responses in our population, with frequencies as high as those induced by major and minor determinants of penicillin [46]. The results for quinolones support the results of different studies indicating an increasing tendency [47-50].

It is relevant to note that in our study, NSAIDs, followed by BLs, were the group of drugs most frequently involved in reactions reported by patients. This contrasts with the findings of a number of publications reporting that BLs are the most frequent drugs involved in DHRs and that NSAIDs are the third most common [46,51-53]. Nevertheless, Messaad et al [13] also found that NSAIDs were the most frequent cause of DHRs, with a total of 91% of all drugs inducing a positive response, including aspirin, paracetamol, and other NSAIDs. Once we had established the final diagnosis, these differences between the drugs involved actually increased and we found that most patients who consulted for reactions attributed to NSAIDs were diagnosed as allergic, with the most frequent hypersensitivity reaction being urticaria and/or angioedema due to cross intolerance, as previously reported [30]. In the case of BLs, however, a substantial proportion (>90%) of patients in this group had good tolerance after completing the evaluation. This is again consistent with the data of Messaad et al, with 8% of cases of allergy to BLs being confirmed by DPT.

We observed a decrease in reactions produced by penicillin and an increase in those induced by amoxicillin, confirming the tendency observed since the 1980s [29]. Patterns of consumption are in part responsible for the allergy response observed to clavulanic acid [46]. Also of interest was the increase in reactions produced by radiocontrast media and the decrease in reactions due to sulfonamides.

A substantial number of cases in our series were diagnosed by clinical history. This can be explained by the high number of patients allergic to NSAIDs, most of whom are eventually diagnosed as having cross intolerance. Although clinical history has been claimed not to be reliable in cases of hypersensitivity to NSAIDs, we have shown that the differences with results reported by other studies may be due to the number of episodes experienced by the patient [30]. In our study, the patients had a mean of 1.13 (0.36) episodes.

Although the data provided do not reflect prevalence, they are nevertheless obtained from a population referred to our center without any kind of restriction or filter. They are, therefore, indicative of the pattern of response of the population over a defined period. We have confirmed that DHRs constitute an important health problem in terms of number of patients evaluated and have detected an increase in allergies due to NSAIDs, quinolones, and iodinated contrast media. Diagnosis required DPT in 30% of cases. In fact, the importance of skin testing decreased over the 6-year study period, probably because of the decrease in patients allergic to BLs and the increase in patients allergic to NSAIDs and quinolones.

Acknowledgments

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