

The Epidemiology of Drug Allergy-Related Consultations in Spanish Allergology Services: *Alergológica-2005*

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■ Abstract

Background: Allergic reactions to drugs constitute one of the most frequent reasons for consultations in Allergology services with an increasing prevalence in recent years.

Objectives: To describe the results of the *Alergológica-2005* study on the clinical characteristics of patients consulting for suspected drug allergies.

Methods: *Alergológica-2005* was a descriptive, cross-sectional, prospective, observational study undertaken with 4991 patients treated for the first time in Allergology services in Spain.

Results: Seven hundred thirty-two patients (mean age 41.4 ± 19.4 years) presented for drug allergies (62% females, 38% males). Diagnosis was confirmed in 26.6% of cases and rejected in 37.2%. Seventy five percent reported only cutaneous symptoms and 10% anaphylaxis. Forty-seven percent of reactions were caused by β -lactams (63% of which were due to amoxicillin), 29% by nonsteroidal anti-inflammatory drugs (NSAIDs) and 10% by pyrazolones. Sixty nine children were treated for this reason, 8 of whom were diagnosed as drug allergic (5 to β -lactams, 2 to NSAIDs and 1 to pyrazolones).

Conclusions: Drug allergies are the third most important reason behind consultations in Allergology services, after bronchial asthma and rhinitis. Females are predominantly affected and the β -lactams, NSAIDs and pyrazolones are the 3 drug families most responsible.

Key words: Drug hypersensitivity. Epidemiology.

■ Resumen

Antecedentes: Las reacciones alérgicas a medicamentos constituyen una de las causas más frecuentes de consulta en los Servicios de Alergia, con prevalencia creciente en los últimos años.

Objetivos: Describir los resultados del estudio *Alergológica-2005* sobre las características clínicas de los pacientes que consultaron por sospecha de alergia a medicamentos.

Métodos: *Alergológica-2005* fue un estudio descriptivo, transversal, prospectivo, observacional, que se realizó en 4991 pacientes atendidos por vez primera en los Servicios de Alergología de España.

Resultados: 732 pacientes (edad media $41,4 \pm 19,4$ años) consultaron por alergia a medicamentos (62% mujeres, 38% hombres). El diagnóstico se confirmó en el 26,6% de los casos y se descartó en el 37,2%. El 75% refería sólo síntomas cutáneos y el 10% anafilaxia. El 47% de las reacciones fueron causadas por betalactámicos (el 63% de las mismas por amoxicilina), el 29% por antiinflamatorios no esteroideos (AINEs) y el 10% por pirazonas. 69 niños consultaron por este motivo, siendo diagnosticados como alérgicos a medicamentos 8 de ellos (5 betalactámicos, 2 AINEs y 1 pirazonas).

Conclusiones: La alergia a medicamentos constituye el tercer motivo de consulta en los Servicios de Alergia tras el asma bronquial y la rinitis. Afecta predominantemente a mujeres, siendo los betalactámicos, AINEs y pirazonas las tres principales familias de fármacos responsables.

Palabras clave: Hipersensibilidad a fármacos, epidemiología.

Introduction

Adverse reactions to drugs are frequent occurrences and, in many cases, are difficult to avoid, as the result of the use of drugs in the treatment of patients. These secondary adverse effects to drugs are most commonly experienced by hospitalized patients. They affect 19% of in-patients and also constitute one of the most important causes of hospital admissions (3-6%) [1]. However, in the general population there is a lack of reliable epidemiologic data regarding the prevalence of drug allergies. In a cross-sectional study carried out in Portugal [2] in an adult population, the prevalence of self-reported drug allergy was 7.8%.

In general allergic reactions to drugs are immunologically mediated if they show the following characteristics: 1) they occur in a small number of patients; 2) they require prior exposures to a particular drug or similar drugs; 3) they begin rapidly following exposure; and 4) they produce symptoms usually associated with immunological reactions [3].

Allergic reactions represent 6% to 10% of all adverse reactions [4]. Indeed, the general risk of an allergic reaction to the majority of drugs is between 1% and 3% [3, 5, 6]. These data account for the large number of suspected drug allergy-related consultations in Allergy services.

The aim of the present study is to describe the data related to the patients consulting in Spain for drug allergies within the *Alergológica-2005* study.

Material and methods

The materials and methods of the *Alergológica-2005* study have been described in the preceding article in this monographic issue [7].

The description of the quantitative variables is given using means and standard deviations when distribution was normal, and in other cases using medians and interquartile ranges. Qualitative variables are described in percentages.

The means of continuous variables were compared using the Student *t* test. Qualitative variables were compared using the Chi-square test with Yates correction when necessary. In all cases comparisons were two-tailed and *P* values of <0.05 were taken as statistically significant.

Results

Seven hundred thirty-two patients consulted for suspected drug allergies. Females (62%) clearly outnumbered males (38%) ($P < .005$). The average age of these patients was 41.4 ± 19.4 years, which made them older than the general sample (32.11 ± 18.4) ($P < .001$).

Patients were mainly referred by the family doctor (61%), 8% on their own initiative and 28% by other specialists, the majority of whom were pediatricians (25%), emergency services (13%) and anesthetists (9%).

The patients consulting for drug allergies reported lower percentages of family histories of asthma (27% vs. 17%) ($P < .001$), rhinitis (31% vs. 19%) ($P < .001$), conjunctivitis (12% vs. 7%) ($P < .001$) and food allergies (4% vs. 2%) ($P < .05$) than the rest of the patients in the *Alergológica* study. However, the patients with drug allergies had a higher percentage of family histories of drug allergies (16% vs. 7%) ($P < .001$).

Regarding atopic family histories, the data are the same. Patients with drug allergies less frequently presented with asthma (13% vs. 10%) ($P < .05$), rhinitis (22% vs. 15%) ($P < .001$) and conjunctivitis (11% vs. 6%) ($P < .001$) than the general sample. In contrast, a history of drug allergy was more common in the study group (18% vs. 2%) ($P < .001$).

Patients who consulted for drug allergies had a greater prevalence of associated illnesses in comparison with the rest of the *Alergológica* study for all the groups of disorders considered ($P < 0.001$ for all comparisons) as shown in Table 1.

Specific data on consultations for drug allergies

The diagnosis of drug allergy was confirmed in 26.6% of patients and was rejected 37.2% of cases. Therefore, a suspected diagnosis was established in 36.2% of patients.

The mechanisms of allergic reactions were immediate in 65% of cases, delayed in 7%, late in 17% and others in 12%.

The median of the time elapsed between the first reaction and consultation was 20 months with an interquartile range of 6 to 60 months. The median of the time elapsed since the last reaction and consultation was 90 days with an interquartile range of 30 to 365 days.

Table 1. Associated Disorders in Patients Consulting for Drug Allergies

	Drug Allergies 2005	<i>Alergológica-2005</i>	<i>Alergológica-1992</i>
Hypertension	14%	5%	10%*
Diabetes	4%	1%	3%
Hypercholesterolemia	11%	5%	7%*
Rheumatic Disorders	10%	3%	7%
Cardiopathies	5%	2%	
Gastroesophageal Reflux	5%	3%	
Others	26%	14%	21%

* indicates a statistically significant difference ($P < .05$) between the 2005 and 1992 data.

Table 2. Clinical Manifestations of Drug Allergies

	Drug Allergies 2005	Drug Allergies 1992
Exclusively Cutaneous	75%	79%
Urticaria	72%	72%*
Angioedema	42%	
Fixed Exanthema	2%	6%
Steven-Johnson Syndrome	1%	1%
Eczema	6%	2%
Anaphylaxis	10%	15%†
Asthma	5%	6% (together with rhinitis)
Rhinitis	2%	
Fever	0.4%	6%**
Others	13%	2%

* indicates that no distinction was made between urticaria and angioedema and so were included in the same category.

† indicates a statistically significant difference ($P < .05$) between the 2005 and 1992 data.

Table 3. Drugs Causing Reactions Leading Patient Consultations

	Drug Allergies 2005	Drug Allergies 1992
β-lactams:	47%	55%†
Penicillin	13%	28%
Amoxicillin	29%	25%*
Other Penicillin Derivatives	3%	
Cephalosporins	2%	2%
NSAIDs	29%	24%
Pyrazolones	10%	16%†
Local Anesthetics	6%	3%†
Quinolones	3%	1%†
Sulfonamides	3%	7%†
Macrolides	3%	3%
Aminoglycosides	2%	3%
Iodinated Contrasts	2%	< 1%
Tetracyclines	1%	3%†
Vitamins	1%	1%
Hormones	1%	
Other Blood Derivatives	1%	< 1%
General Anesthetics	1%	1%
Others	11%	9%

* indicates that amoxicillin was included in the category of penicillin derivatives.

† indicates a statistically significant difference ($P < 0.05$) between the 2005 and 1992 data.

Seventy five percent of patients had exclusively cutaneous symptoms, whilst 10% experienced anaphylaxis. Within the group of patients showing exclusively cutaneous symptoms, 72% presented with urticaria and 42% with angioedema as shown, together with the remaining manifestations, in Table 2.

The route of administration was principally oral (77%).

Etiologic agents

Eighty-two percent of patients consulted for allergy to only one drug, 14% to 2 drugs and the remaining 4% to 3 or more drugs.

The drugs responsible for the allergic reactions are listed

Table 4. Summary of the Data From Patients Consulting for Allergy to Only One Drug*

	Time Since First Reaction (months)	Time Since Last Reaction (days)	Number of Reactions	Diagnosis	Diagnostic Tests
β -lactams	Median 24 Range 1-99	Median 120 Range 1-999	Median 1 Range 1-12	Confirmed 29% Rejected 42% Suspected 29%	Immediate Skin Tests 85% Delayed Intra-dermal Skin Tests 10% Epicutaneous Tests 9% Challenge Tests 58% Immunoglobulin Tests 35% Other <i>in vivo</i> Tests 21%
NSAIDs	Median 16 Range 1-99	Median 60 Range 1-999	Median 2 Range 1-12	Confirmed 34% Rejected 20% Suspected 46%	Immediate Skin Tests 43% Delayed Intra-dermal Skin Tests 5% Epicutaneous Tests 12% Challenge Tests 65% Immunoglobulin Tests 0% Other <i>in vivo</i> Tests 3%
Pyrazolones	Median 22 Range 1-99	Median 180 Range 3-999	Median 1 Range 1-10	Confirmed 50% Rejected 5% Suspected 45%	Immediate Skin Tests 87% Delayed Intra-dermal Skin Tests 8% Epicutaneous Tests 3% Challenge Tests 49% Immunoglobulin Tests 0% Other <i>in vivo</i> Tests 8%
Other Antibiotics	Median 24 Range 1-99	Median 72 Range 1-999	Median 2 Range 1-15	Confirmed 36% Rejected 24% Suspected 39%	Immediate Skin Tests 67% Delayed Intra-dermal Skin Tests 7% Epicutaneous Tests 26% Challenge Tests 56% Immunoglobulin Tests 2% Other <i>in vivo</i> Tests 3%
Various	Median 22 Range 1-12	Median 88 Range 1-999	Median 1 Range 1-15	Confirmed 17% Rejected 55% Suspected 28%	Immediate Skin Tests 79% Delayed Intra-dermal Skin Tests 9% Epicutaneous Tests 27% Challenge Tests 49% Immunoglobulin Tests 3% Other <i>in vitro</i> Tests 0%

* NSAIDs indicates non-steroidal antiinflammatory drugs.

in Table 3. As was the case in the *Alergológica-92* study, the β -lactams continued to be the principal cause of consultations for allergic reactions to drugs (47%). Amoxicillin was the cause behind 29% of consultations and approximately 63% of the reactions caused by β -lactams, while penicillin represented less than 30% of the reactions due to β -lactams. Together with the reactions caused by non-steroidal antiinflammatory drugs (NSAIDs) (29% of all consultations) and by pyrazolones (10% of the total), these 3 drug families were responsible for 86% of the reactions attributed to drug allergies.

In the diagnosis of these patients the most frequently used tests were immediate skin tests (68%) and oral challenge.

Given that in 18% of cases patients consulted for reactions caused by 2 or more drugs, we have summarized in Table 4 the most important data from those patients who consulted for reactions

caused by only one drug. In this way, any overlap between data, diagnoses and diagnostic examinations was avoided.

Drug allergies in children

The 69 children (under the age of 14) studied represented 9.8% of the patients in comparison with 18.37% of the general sample ($P < .0001$). In these children, 8 cases of drug allergy were confirmed – 5 with β -lactams (4 with amoxicillin and 1 with penicillin derivatives), 2 with NSAIDs and 1 with pyrazolones. The diagnosis was rejected in 58% of cases and suspected in 30% of cases. In comparison with adults, a lower percentage of cases was confirmed in children whilst a greater number of cases was excluded than in the adults ($P < .001$).

The children exhibited a higher percentage of delayed reactions than the adults (15% vs. 6%, respectively) ($P < .05$) although there were no differences between the 2 groups for immediate (54%), late (12%) and other (19%) reactions.

The symptoms presented by the children were almost exclusively cutaneous (92%). Only 1 case of anaphylaxis was recorded, another of asthma and 3 with other symptoms. Within the cutaneous symptoms, 71% of patients developed urticaria and 29% angioedema.

The β -lactam antibiotics were the main cause of consultations for suspected drug-allergy related reactions in children and were responsible for 81% of all cases. In particular, amoxicillin alone was responsible for practically two thirds of all cases. In second place were the NSAIDs which were responsible for 13% of reactions with the remaining drugs only accounting for 1 or 2 cases.

Discussion

Allergy to drugs constitutes one of the most specific aspects of the specialty of Allergology. It may cause mild symptoms such as skin rash or clinical conditions with high mortality such as toxic epidermic necrolysis [3]. Not studying this phenomenon and either over- or under-diagnosing it involves different risks for patients: anaphylactic shock, 13% of the cases of which are due to drug allergies [8] with a prevalence of death of 0.3/10⁶ inhabitants [9], increases in treatment and/or hospitalization costs, the use of alternative drugs and in general greater cost [10] and greater risk of inducing antibiotic resistance, among others.

Probably as a result of the reasons mentioned above, drug allergies constitute, as was the case in the similar epidemiologic study launched by the SEAIC, *Alergológica*-92 [11], the third cause of consultations after rhinoconjunctivitis and bronchial asthma, but with a slightly higher percentage (14.7%) than was found in this earlier study (12.6%) ($P < .005$).

Allergic reactions to drugs are a subgroup of adverse reactions to drugs. As a result, the risk factors for developing adverse reactions to drugs (age, female sex, extremes of age, genetic predisposition, multiple comorbid conditions, concurrent use of multiple medications, etc.) [12] are shared by allergic drug reactions. The ratio female:male is practically 2:1. This is essentially the same as that recorded in the *Alergológica*-92 (63% females vs. 37% males) [13]. Similarly, the proportion of females in this drug allergy group is higher than in the general sample (56%) ($P < .05$). This clear predominance of adverse reactions to drugs is common in practically all studies on drug allergy, as is the confirmation of the higher risk for drug allergies among females [2, 4].

The patients in this group were older than the average age of participants in the whole study. This seems to be related to the lower number of children among the patients who consulted for drug allergies – 9.8% of patients in comparison with 18.37% of the general sample (figures similar to the 12.5% from *Alergológica*-92) [11]. This age distribution is confirmed by 2 facts. Firstly, the rare occurrence of allergies in pediatric patients [1] and secondly, the greater occurrence of drug allergies in elderly patients [13].

These patients had clearly fewer family or personal histories of atopy than the remaining participants in the *Alergológica* study. These data seem to confirm the fact that drug allergies do not seem to be increasing in atopic populations [14, 15].

The situation, however, is very different in the case of patients with personal or family histories of drug allergies. There is a much higher number of these in our study group. This confirms the substantial increase in risk (up to 15 times greater) of allergic reactions to antibiotics in children with parents who are allergic to these drugs [16].

Overall, patients who consulted for drug allergies suffered more frequently from associated disorders than the rest of the sample studied (Table 1). This fact, together with older age, more admissions to hospital for reasons other than possible drug allergies which also involves longer hospital stays (data not shown), leads to a higher consumption of drugs which facilitates the appearance of a greater number of adverse drug reactions and amongst these, allergic reactions [14].

One interesting fact prior to the consultation is the long time interval between the last reaction and the allergic study. At least 25% of patients waited for more than 1 year after experiencing the reaction before consulting. This may lead to a high percentage of false negatives in the diagnostic process [17] and favor the use of potentially more dangerous tests such as the challenge test.

In our study group, both in children and adults, cutaneous symptoms were the most frequent. These symptoms are equally the most frequent in drug allergic reactions [2, 4, 18, 19] as they may occur in 2.3% of all drug administrations and are especially common in certain drugs such as amoxicillin [20].

The β -lactams, NSAIDs and pyrazolones as single allergens are the 3 groups of drugs that cause the majority of adverse drug reactions, as was found in *Alergológica*-92 [11] where they were responsible for 95% of reactions. With the exception of the pyrazolones, due to the high consumption of methamizol in Spain, the other data agree with most published articles on adverse drug reactions, especially with cutaneous symptoms, in which the β -lactams, NSAIDs and sulfonamides/trimethoprim are the main etiologic agents [4, 21-23]. In these 3 groups, amoxicillin and in general the aminopenicillins are the drugs responsible for most of these reactions [20, 23, 24], as was also the case in our sample.

The remaining drug families are quantitatively much less important and in comparison with 1992 there has been a decrease in sulfonamides (3% vs. 7%), and tetracyclines (1% vs. 3%), probably as a result of the continuing decrease in their use and the increase in the use of local anesthetics (6% vs. 3%) and quinolones (3% vs. 1%), with this last in particular being ever more frequently used in daily practice. With regard to the NSAIDs, it is worthy of note that of the 220 cases recorded, 120 were caused by 1 NSAID and 100 cases by several. This multiplicity of reactions caused by NSAIDs is a frequently reported fact in other series of reactions to these drugs [25].

In conclusion, drug allergies are the third most frequent reason for consultations in Allergology services. Their prevalence is clearly higher in women (62%). The commonest clinical manifestations are cutaneous and these appear with no other manifestations in 75% of cases. Three drug families are responsible for 86% of reactions: β -lactams (47%),

NSAIDs (29%) and pyrazolones (10%). Finally, the fact that the diagnosis was suspected in 36.2% of cases only serves to underline the need for allergy studies in these patients.

References

- Lazarou J, Pomeranz BH, Corey PN. Incidence of adverse drug reactions in hospitalized patients: a meta-analysis of prospective studies. *JAMA*. 1991;266:2847-51.
- Gomes E, Cardoso MF, Praça F, Gomes L, Mariño E, Demoly P. Self-reported drug allergy in a general adult Portuguese population. *Clin Exp Allergy*. 2004;34:1597-1601.
- Demoly P, Hillaire-Buys D. Classification and epidemiology of hypersensitivity drug reactions. *Immunol Allergy Clin N Am*. 2004;24:345-56.
- de Shazo RD, Kemp S. Allergic reactions to drugs and biological agents. *JAMA*. 1997;278:1895-1906.
- International Rheumatic Fever Study Group. Allergic reactions to long-term benzathine penicillin prophylaxis for rheumatic fever. *Lancet*. 1991;337:1308-10.
- Burke P, Burne SR. Allergy associated with ciprofloxacin. *BMJ*. 2000;320:679.
- Caballero Martínez F. *Alergológica 2005. Methodological Aspects and Sample Characteristics of the Study*. *J Investig Allergol Clin Immunol*. 2009;Vol 19,suppl 2:46.
- Yocum MW, Khan DA. Assessment of patients who have experienced anaphylaxis: a 3 year survey. *Mayo Clin Proc*. 1994;69:16-23.
- Lenler-Petersen P, Hansen D, Andersen M, Toft Sorensen H, Bille H. Drug-related fatal anaphylactic shock in Denmark 1968-1990. A study based on notifications to the committee on adverse drug reactions. *J Clin Epidemiol*. 1995;48:1185-8.
- Preston SL, Briceland LL, Lesar TS. Accuracy of penicillin allergy reporting. *Am J Hosp Pharm*. 1994;51:79-84.
- Alergologica. Alergia a medicamentos. Sociedad Española de Alergología e Inmunología Clínica y Alergia e Inmunología* Abelló SA, editores. Madrid: Nilo Industria Gráfica. 1995.
- Calis KA, Sidaway EN, Young LR. Clinical analysis of adverse drug reactions. In Atkinson AJ, Abernethy DR, Daniels ChE, Detrick RL, Markey SP. *Principles of Clinical Pharmacology* 2nd ed. San Diego: Academic Press. 2007. p. 389-401.
- Lang DM, Vogel NM, Jain A. Epidemiology of medication "allergy" at a tertiary care center [abstract]. *J Allergy Clin Immunol* 2006;117(2 suppl):S138.
- Gadde J, Spence M, Wheeler B, Adkinson NF Jr. Clinical experience with penicillin skin testing in a large inner-city STD clinic. *JAMA*. 1993;270:2456-63.
- Adkinson NF. Risk factor for drug allergy. *J Allergy Clin Immunol* 1984;74:567-72.
- Attaway NJ, Jasin HM, Sullivan TJ. Familial drug allergy [abstract]. *J Allergy Clin Immunol*. 1991;87 [2 suppl]:227.
- Blanca M, Torres MJ, García JJ, Romano A, Mayorga C, de Ramon E, Vega JM, Miranda A, Juarez C. Natural evolution of skin test sensitivity in patients allergic to beta-lactam antibiotics. *J Allergy Clin Immunol*. 1999;103:918-24.
- Barranco P, López-Serrano MC. General and epidemiological aspects of allergic drug reactions. *Clin Exp Allergy*. 1998;28(suppl 4):61-2.
- Ausin A, Moreno-Escobosa MC, Alonso E, Ibañez MD, Muñoz MC, Laso MT. Drug allergy in children [abstract]. *Allergy*. 1998;53 (suppl 43):116.
- Bigby M, Jick S, Jick H, Arndt K. Drug-induced cutaneous reactions: a report from the Boston Collaborative Drug Surveillance Program on 15438 consecutive inpatients, 1975 to 1982. *JAMA*. 1986;256:3358-63.
- Bigby M. Rates of cutaneous reactions to drugs. *Arch Dermatol*. 2001;137:765-70.
- Roujeau JC, Robert S. Medical Progress: Severe adverse cutaneous reactions to drugs. *N Engl J Med*. 1994;331:1272-85.
- Hunziker Th, Künzi UP, Braunschweig S, Zehnder D, Hoigné R. Comprehensive hospital drug monitoring (CHDM): adverse skin reactions, a 20-year survey. *Allergy*. 1997;52:388-93.
- Sonntag MR, Zoppi M, Fritschy D, Maibach D, Stocker F, Sollberger J, Buchli W, Hess T, Hoigné R. Exanthema during frequent use of antibiotics and antibacterial drugs (penicillin, especially aminopenicillin, cephalosporin and cotrimoxazole) as well as allopurinol: results of the Berne Comprehensive Hospital Drug Monitoring program. *Schweiz Med Wochenshr*. 1986;116:142-5.
- Gamboa P, Sanz ML, Caballero MR, Urrutia I, Antepará I, Esparza R, de Weck AL. The flow-cytometric determination of basophil activation induced by aspirin and other non-steroidal anti-inflammatory drugs (NSAIDs) is useful for in vitro diagnosis of the NSAID hypersensitivity syndrome. *Clin Exp Allergy*. 2004;34:1448-57.

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