

Drug-Induced Anaphylaxis Survey in Portuguese Allergy Departments

E Faria,¹ J Rodrigues-Cernadas,² Â Gaspar,³ C Botelho,² E Castro,² A Lopes,⁴ E Gomes,⁵ D Malheiro,⁶ S Cadinha,⁶ S Campina-Costa,⁷ M Neto,⁸ N Sousa,¹ R Rodrigues-Alves,⁹ A Romeira,¹⁰ J Caiado,⁴ M Morais-Almeida,³ Portuguese Society of Allergology and Clinical Immunology (SPAIC) Drug Allergy Interest Group

¹Immunoallergology Department, Hospital Universidade de Coimbra, Centro Hospital e Universitário de Coimbra, Coimbra, Portugal

²Immunoallergology Department, Centro Hospitalar São João, Porto, Portugal

³Immunoallergology Department, Hospital CUF Descobertas, Lisboa, Portugal

⁴Immunoallergology Department, Hospital de Santa Maria, Centro Hospitalar Lisboa Norte, Portugal

⁵Immunoallergology Department, Hospital Maria Pia, Centro Hospitalar do Porto, Portugal

⁶Immunoallergology Department, Centro Hospitalar de Vila Nova de Gaia/Espinho, Portugal

⁷Immunoallergology Department, Hospital de Egas Moniz, Centro Hospitalar Lisboa Ocidental, Portugal

⁸Immunoallergology Department, Hospital Pulido Valente, Centro Hospitalar Lisboa Norte, Portugal

⁹Immunoallergology Department, Hospital Divino Espírito Santo, Ponta Delgada, Açores, Portugal

¹⁰Immunoallergology Department, Hospital de Dona Estefânia, Centro Hospitalar Lisboa Central, Portugal

■ Abstract

Background and Objective: Drug-induced anaphylaxis is an unpredictable and potentially fatal adverse drug reaction. The aim of this study was to identify the causes of drug-induced anaphylaxis in Portugal.

Methods: During a 4-year period a nationwide notification system for anaphylaxis was implemented, with voluntary reporting by allergists. Data on 313 patients with drug anaphylaxis were received and reviewed. Statistical analysis included distribution tests and multiple logistic regression analysis to investigate significance, regression coefficients, and marginal effects.

Results: The mean (SD) age of the patients was 43.8 (17.4) years, and 8.3% were younger than 18 years. The female to male ratio was 2:1. The main culprits were nonsteroidal anti-inflammatory drugs (NSAIDs) (47.9% of cases), antibiotics (35.5%), and anesthetic agents (6.1%). There was a predominance of mucocutaneous symptoms (92.2%), followed by respiratory symptoms (80.4%) and cardiovascular symptoms (49.0%). Patients with NSAID-induced anaphylaxis showed a tendency towards respiratory and mucocutaneous manifestations. We found no significant associations between age, sex, or atopy and type of drug. Anaphylaxis recurrence was observed in 25.6% of cases, and the risk was higher when NSAIDs were involved.

Conclusions: NSAIDs were the most common cause of anaphylaxis in this study and were also associated with a higher rate of recurrence. We stress the need for better therapeutic management and prevention of recurring episodes of drug-induced anaphylaxis.

Key words: Anaphylaxis. Drug hypersensitivity. Notification. Portuguese survey.

■ Resumen

Antecedentes: La anafilaxia inducida por medicamentos es una reacción adversa impredecible y potencialmente fatal. El objetivo de este estudio fue identificar las causas de la misma en Portugal.

Método: Durante un periodo de 4 años fue desarrollado un sistema de notificación nacional de anafilaxia enfocado al informe voluntario de los alergólogos. Se recopilaron 313 casos de pacientes con anafilaxia por medicamentos. El análisis estadístico incluyó test de distribución y regresión logística múltiple para analizar la significación y los coeficientes de regresión y efectos marginales.

Resultados: La edad media de los pacientes fue de 43.8 ± 17.4 años, 8.3% menores de 18 años. La relación mujer/varón fue de 2:1. El grupo más frecuentemente implicado fue el de los analgésicos antiinflamatorios no esteroideos (AINEs), seguido de los antibióticos y anestésicos

en 47.9%, 35.5% y 6.1% de los casos respectivamente. Se observó un predominio de los síntomas mucocutáneos (92.2%), seguidos de los respiratorios (80.4%) y cardiovasculares (49.0%). Los pacientes con anafilaxia por AINEs mostraban más síntomas respiratorios y mucocutáneos. No se encontró asociación entre edad, género y atopía con los diferentes grupos de medicamentos. La recurrencia de anafilaxia se observó en el 25.6% de los casos, con un riesgo incrementado cuando los AINEs eran los responsables.

Conclusiones: En este estudio, los AINEs fueron los medicamentos más frecuentemente implicados en las reacciones de anafilaxia y mostraron más frecuencia de reincidencia de las reacciones. Es importante evaluar bien los tratamientos y prevenir la reincidencia de anafilaxia por medicamentos.

Palabras clave: Anafilaxia. Hipersensibilidad a medicamentos. Encuesta portuguesa.

Introduction

Adverse drug reactions are a serious public health problem in both inpatient and outpatient settings. They are associated with high morbidity and socioeconomic costs and are also potentially fatal, with an inpatient mortality of 0.05% to 0.19% [1]. Approximately 20% of adverse drug reactions, which are mediated by allergic or nonallergic mechanisms, are designated hypersensitivity reactions.

Anaphylaxis is a severe, potentially fatal event. It is an acute systemic hypersensitivity reaction with simultaneous involvement of several organs, particularly the skin, the respiratory tract, and the gastrointestinal and/or the cardiovascular system. The severity of the reaction varies, and is classified as grade I to IV on the Ring and Messmer scale [2]. The diagnostic and treatment criteria for anaphylaxis were recently revised to standardize the concepts used [3,4].

Anaphylactic reactions associated with drugs can be due to IgE antibody-mediated immunological reactions to the drug or to a metabolite or excipient. Reactions with similar symptoms, however, can be non-immunologically mediated. This condition was formerly called non-immunological anaphylaxis [4].

According to a study of primary healthcare data from the United Kingdom the annual incidence of anaphylaxis is 8.4 cases per 100 000 individuals in the general population, and the most frequent causes are insect venoms (32%), drugs (30%), and foods (22%) [5]. In a recent report based on the Latin American Survey of Anaphylaxis, the main causes of anaphylactic reactions were drugs (31.2%), foods (23.3%), and insect stings (14.9%) [6].

In a retrospective study performed in an inpatient immunoallergy department in Portugal, the main agents causing anaphylactic reactions in adults were drugs (66%), iodinated contrast media (ICM) (19%), foods (13%), and hymenoptera venoms (2%) [7]. Finally, in 2 studies of outpatient children in Portugal, the most common causes of anaphylaxis were found to be foods, drugs, and latex [8,9].

Geographic factors and prescription patterns influence the rate of anaphylaxis to different classes of drugs.

A recent meta-analysis of 18 international epidemiological studies on drug-induced anaphylaxis in adults and children published from 1994 to 2009 reported that it was impossible to quantify the rate and mortality of drug-induced anaphylaxis because of differences in methodology and definitions of anaphylaxis [10]. In the majority of cases diagnosis was based on clinical examination and epidemiological data rather than on

confirmation of a cause-effect relationship or the identification of underlying immunological mechanisms. A predominance of cases were seen in males aged under 15 years and the highest rate was seen in adults aged 55 to 84 years (3.8/100 000 individuals) [10]. Drugs are considered the main trigger of adult-age anaphylaxis, particularly in individuals aged over 65 years [4,11]. Drugs were reported as the main cause of fatal anaphylaxis in this age group in the United Kingdom, New Zealand, and Australia [10].

The above meta-analysis also concluded that penicillin and general anesthetic agents were the most common causes of IgE-mediated anaphylactic reactions, while nonsteroidal anti-inflammatory drugs (NSAIDs) and ICM were the most common causes of non-immunological anaphylaxis [10]. In addition, inpatients have also been found to be at greater risk of anaphylaxis due to streptokinase and plasma and its derivatives and at lower risk of anaphylaxis due to NSAIDs and antibiotics [12].

The difficulty in confirming a diagnosis of anaphylaxis lies in the lack of standardized tests for studying reactions to the majority of drugs and the limitations of challenge tests in patients with potentially fatal reactions.

The severity of the anaphylactic reaction is related to the type of drug involved, the individual's degree of sensitivity, and other factors such as age, genetic background, co-infection or inflammatory disease, exercise, stress, and concomitant treatment [4,9]. Asthma and other chronic respiratory diseases, cardiovascular disease, mastocytosis, and the co-administration of β -blockers or angiotensin-converting-enzyme inhibitors seem to be risk factors for severe or fatal reactions [3,13,14].

The true rate of drug anaphylaxis in Portugal is unknown as cases are not systematically registered, but a recent publication of drug-induced anaphylaxis cases reported to the Portuguese Pharmacovigilance Authority shows a tendency towards an increase in recent years [15].

The aim of this study was to contribute to a better understanding of the causes of drug-induced anaphylaxis in Portugal based on a study of anaphylaxis cases reported by immunoallergy departments over a 4-year period.

Methods

The Portuguese Society of Allergy and Clinical Immunology (SPAIC) implemented a national anaphylaxis notification system over a 4-year period (January 2007-December 2010).

Anaphylaxis was diagnosed according to the criteria published by the American Academy of Asthma, Allergy and Immunology (AAAAI), the European Academy of Allergy and Clinical Immunology (EAACI), and the World Allergy Organization (WAO) [3,4].

All members of SPAIC were invited to participate in the project and asked to use a specially designed questionnaire (Figure 1) to report all cases of drug-induced anaphylaxis (“at least 1 episode of a severe systemic reaction”) seen in their departments. The questionnaires were sent by letter, fax, e-mail, or through an online system on the SPAIC website. All notifications received were evaluated and validated by

members of the SPAIC Drug Allergy Interest Group. After a preliminary data analysis, it was decided to complement this questionnaire with further data. When necessary, clarification was sought from the notifying person.

A diagnosis of drug-induced anaphylaxis was confirmed by allergists based on the consensus statement published by the European Network of Drug Allergy - ENDA/EAACI [16].

The information in the questionnaire was complemented with further data in a subsample of 282 cases (90.0%). Additional information included drug administration route, time between drug administration and onset of symptoms, setting (inpatient or outpatient), and the presence of atopy.

Population

Questionnaires containing information on 313 patients with a clinical history of drug-induced anaphylaxis were received from 41 Portuguese immunoallergology specialists.

Statistical Analysis

The results are given as the frequency of positive answers relative to the total number of valid responses. Multivariate logistic regression analysis was used to evaluate significance ($P < .05$), regression coefficients, and marginal effects. Significance was also evaluated using χ^2 distribution tests.

Results

We analyzed the cases of 313 patients.

Forty percent of the population lived in the north of Portugal, 38% in the south, 19% in the center, and 3% in the Azores and Madeira.

The mean (SD) age of the patients was 43.8 (17.4) years (range, 2-89 years); 8.3% were aged ≥ 4 -18 years; 21.4%, ≥ 18 -35 years; 58.5%, ≥ 35 -65 years; and 11.8% 65 years or older.

There was a majority of female patients (66.1%; male to female ratio of 1:2). In the youngest age group, however, there were more males than females (ratio of 1.9:1). Forty-three percent of the population had a history of allergic disease, 18.8% had asthma, and 31.6% had rhinitis.

The mean age at the time of the first anaphylactic episode was 39.0 (18.2) years (range, 2-89 years). Table 1 shows the causes of drug-induced anaphylaxis by age group.

The 3 main drug groups involved were NSAIDs, antibiotics, and anesthetic agents. Tables 2 and 3, respectively, show the NSAIDs and antibiotics involved according to age.

The 19 cases of anaphylaxis induced by anesthetic agents were all reported in adults. Local anesthetics were involved in 2 cases and the anesthetic agent was not identified in 3 cases. In the remaining 14 cases, the general anesthetics identified were neuromuscular blocking agents (NMBAs) (52.6%), propofol (10.5%), and midazolam (10.5%).

Table 4 shows the characteristics of the patients with anaphylaxis induced by NSAIDs, β -lactam antibiotics, and general anesthetics.

No statistically significant differences were found between age, atopy, or asthma and type of drug in any of the cases, but there was a very high rate of reactions to general

Anaphylaxis Notification Report	
Sociedade Portuguesa de Alergologia e Imunologia Clínica	
Patient identification	
Name: _____ (initials)	
Date of birth:/...../.....	Gender: ____ (male / female)
Residence:	
Cause of anaphylaxis	
Food allergy: ____ (yes / no). If yes, which?.....	
Drug allergy: ____ (yes / no). If yes, which?.....	
Latex allergy: ____ (yes / no). Latex-fruit syndrome: ____ (yes / no)	
Insect sting allergy: ____ (yes / no). If yes, which?.....	
Cold / other physical agent: ____ (yes / no). If yes, which?.....	
Idiopathic anaphylaxis: ____ (yes / no)	
Other cause: ____ (yes / no). If yes, which?.....	
Description(s) of reaction(s):	
.....	
Date of anaphylaxis (first episode):/...../.....	
Number of anaphylaxis episodes:.....	
Treatment	
Adrenaline: ____ (yes / no). Other therapy: ____ (yes / no) . If yes, which?.....	
Emergency room visit: ____ (yes / no).	
Hospitalisation: ____ (yes / no). Fatal outcome: ____ (yes / no).	
Prescription of adrenaline auto-injector: ____ (yes / no).	
Adrenaline auto-injector use: ____ (yes / no).	
Personal history of allergy	
Asthma: ____ (yes / no). Other allergy: ____ (yes / no) . If yes, which?.....	
Name of notifier:	
Date of notification:/...../..... Contact (e-mail):	
Imunoallergology Department:	
Send to:	
SPAIC - Sociedade Portuguesa de Alergologia e Imunologia Clínica	
R. Manuel Rodrigues da Silva, 7C - Escritório 1, 1600-503 Lisboa, Portugal	
Fax: +351 217152428 e-mail: spaic@sapo.pt	

Figure 1. Anaphylaxis notification report questionnaire.

anesthetics in females, with a male to female ratio of 1:4.7. Atopy was found in a large percentage of cases (43.1%), but was not a risk factor for anaphylaxis to any of the three groups of drugs.

The clinical manifestations were mucocutaneous in 92.2% of patients, respiratory in 80.4%, cardiovascular in 49.0%, and gastrointestinal in 14.8%. Loss of consciousness occurred in 13.5% of patients. Simultaneous involvement of 3, 4, and 5 organ systems was observed in 33.5%, 14.4%, and 2.9% of cases, respectively.

Time between drug administration and onset of clinical manifestations varied between 5 minutes and 8 hours. The majority of patients (88.4%) experienced symptoms within 60 minutes, and 53.0% of the total group experienced symptoms in the first 15 minutes. In 6% of cases, the anaphylactic reactions, all related to NSAIDs, were reported after 2 hours: 2 patients experienced a reaction 4 hours after the administration of nimesulide and another 2 patients experienced a reaction (1 to paracetamol and 1 to etoricoxib) after almost 8 hours.

In 45.0% of cases, the anaphylactic reactions occurred in a hospital setting. The route of administration was oral in 64.4% of cases, intravenous in 23.3%, intramuscular in 11.1%, and subcutaneous in 0.4%. There was 1 case of rectal administration and another of a reaction following intradermal testing to amoxicillin.

Emergency hospital assistance was required in 78.3% of patients and 31.5% of these were admitted to hospital. Only 47.7% of patients received treatment with epinephrine. None of these reactions was fatal. In 9.0% of cases an epinephrine auto-injector was used; use of this injector was significantly more common in children ($P=.007$).

The recurrence rate was 25.6%; 73.8% of patients had 2 anaphylactic episodes, 15% had 3, 7.5% had 4, and 3.7% had 5. There were no differences in recurrence of anaphylaxis in terms of sex or age. Overall, 58.4% of all cases of recurrence were caused by NSAIDs (62.4% to different cyclooxygenase [COX] 1 inhibitors and 37.6% to the same NSAID), 21.9% by antibiotics, and 11.8% by other drugs (3 by carboplatin, 2 by proton pump inhibitors, 2 by systemic corticosteroids, 1 by lidocaine, 1 by diosmin, and 1 by calcitonin). In 7.9% of cases, recurrence was induced by both NSAIDs and antibiotics.

Anaphylaxis recurrence due to NSAIDs was significantly more common ($P=.036$) and the probability of 2 or more episodes involving NSAIDs was 13.5% higher than with other drugs.

The patients with NSAID-induced anaphylaxis had a lower probability of admission to hospital after 1 episode ($P<.001$), an increased occurrence of associated respiratory and mucocutaneous symptoms (24.6%), and a decreased

Table 1. Causes of Drug-Induced Anaphylaxis in 313 Patients by Age Group^a

Drugs	All Patients (n=313)	Patients <18 y (n=26)	Patients 18-65 y (n=250)	Patients ≥65 y (n=37)
NSAIDs	150 (47.9)	11 (42.3)	124 (49.6)	15 (40.5)
Antibiotics	111 (35.5)	12 (46.2)	91 (36.4)	8 (21.6)
Anesthetic agents	19 (6.1)	0	15 (6)	4 (10.8)
Cytostatics (carboplatin, 4; oxaliplatin, 3; docetaxel, 1; tamoxifen, 1)	9 (2.9)	1 (3.8)	4 (1.6)	4 (10.8)
Corticosteroids (hydrocortisone, 2; methylprednisolone, 2; betamethasone, 1)	5 (1.6)	1 (3.8)	3 (1.2)	1 (2.7)
Analgesics (clonixin)	5 (1.6)	0	5 (2)	0
PPIs (lansoprazole, 1; omeprazole 1; pantoprazole, 1; esomeprazole, 1)	4 (1.3)	0	4 (1.6)	0
Vitamins (vitamin B ₁₂ , 3; vitamin D ₃ , 1)	4 (1.3)	0	2 (0.8)	2 (5.4)
Iodinated contrast media	3 (0.96)	0	1 (0.4)	2 (5.4)
Vaccines (anti-tetanus in 1 adult; MMR and anti-meningococcal in 1 child)	2 (0.6)	1 (3.8)	1 (0.4)	0
Others ^b	10 (3.2)	0	8 (3.2)	2 (5.4)

Abbreviations: MMR, measles, mumps, and rubella vaccine; NSAIDs, nonsteroidal anti-inflammatory drugs; PPI, proton pump inhibitor.

^aData are presented as number (%) of patients in each group.

^bAtropin, 2; calcitonin, 1; patent blue V, 1; diosmin, 1; hydroxyzine, 1; metoclopramide, 1; colloidal infusion, 1; ranitidine, 1; sulfasalazine, 1.

Table 2. Drugs Responsible for NSAID-Induced Anaphylaxis^a

NSAIDs	All Patients (n=150)	Patients <18 y (n=11)	Patients ≥18 y (n=139)
Preferential COX-1 inhibitors			
ASA	55 (36.7)	4 (36.4)	51 (36.7)
Diclofenac	40 (26.7)	0	40 (28.8)
Ibuprofen	37 (24.7)	7 (63.6)	30 (21.6)
Metamizole	13 (8.7)	0	13 (9.4)
Other (aceclofenac, 1; ketoprofen, 2; ketorolac, 2; dexibuprofen, 1; fentiazac, 1; flurbiprofen, 1; naproxen, 1; propyphenazone, 1)	10 (6.7)	0	10 (7.2)
Weak COX-1 inhibitors			
Paracetamol	2 (1.3)	2 (18.2)	0
Preferential/selective COX-2 inhibitors			
Nimesulide	6 (4)	0	6 (4.3)
Coxibs (parecoxib, 1; etoricoxib, 1)	2 (1.3)	0	2 (1.4)

Abbreviations: ASA, acetylsalicylic acid; COX, cyclooxygenase; NSAID, nonsteroidal anti-inflammatory drug.

^aData are presented as number (%) of patients in each group.

Table 3. Drugs Responsible for Antibiotic-Induced Anaphylaxis^a

Antibiotics	All Patients (n=111)	Patients <18 y (n=12)	Patients ≥18 y (n=99)
β-Lactam antibiotics	90 (81.1)	12 (100)	78 (78.8)
1. Penicillins	67 (60.4)	7 (58.3)	60 (60.6)
1.1. Benzylpenicillins	11 (9.9)	0	11 (11.1)
1.2. Aminopenicillins (amoxicillin, 34; amoxicillin + clavulanic acid, 16; ampicillin, 2)	52 (46.8)	6 (50)	46 (46.5)
1.3. Isoxazolyl penicillins (flucloxacillin)	4 (3.6)	1 (8.3)	3 (3)
2. Cephalosporins	23 (20.7)	4 (33.3)	19 (19.2)
2.1. First-generation (cefazolin, 13; cefatrizine, 1; cephradine, 1)	15 (13.5)	0	15 (15.2)
2.2. Second-generation (cefuroxime, 2; cefoxitin, 1)	3 (2.7)	1 (8.3)	2 (2)
2.3. Third-generation (ceftriaxone, 4; ceftazidime, 1)	5 (4.5)	3 (25)	2 (2)
Quinolones (ciprofloxacin, 7; moxifloxacin, 5; levofloxacin, 1)	13 (11.7)	0	13 (13.1)
Macrolides (clarithromycin, 2; spiramycin, 1)	3 (2.7)	0	3 (3)
Sulphonamides (cotrimoxazole)	3 (2.7)	0	3 (3)
Other (minocycline, 1; vancomycin, 1)	2 (1.8)	0	2 (2)

^aData are presented as number (%) of patients in each group.

Table 4. Characterization of Anaphylaxis by 3 Main Groups of Drugs

Drugs	Mean (SD) Age, y (Range)	Sex	Asthma, % of Patients	Atopy, % of Patients	Mean Time to Reaction (Range)
NSAIDs (n=150)	43.0 (16.6) (3-89)	F: 59% M: 41% Ratio: 1.5:1	27.0	47.5	30 min (5 min-8 h)
β -Lactam antibiotics (n=90)	39.9 (18.2) (4-82)	F: 74% M: 26% Ratio: 2.9:1	16.9	47.8	15 min (5 min-5 h)
General anesthetics (n=17)	52.9 (17.3) (18-78)	F: 82% M: 18% Ratio: 4.7:1	0	20.0	Immediate ^a

Abbreviations: F, female; M, male; NSAIDs, nonsteroidal anti-inflammatory drugs.

^aAll 17 patients experienced intraoperative anaphylaxis.

Table 5. Regression Analysis of Probability of Clinical Symptoms and Recurrence of Anaphylaxis by 3 Main Groups of Drugs

	NSAIDs dy/dx	β -Lactam Antibiotics dy/dx	General Anesthetics dy/dx
Respiratory symptoms	15.5% ^a	-8.4%	-8.8%
Respiratory and mucocutaneous symptoms	24.6% ^b	-1.6%	-13.1%
Cardiovascular symptoms	-16.6%	7.8	37.6% ^b
Recurrence of anaphylaxis	13.5% ^c	-5.0%	-17%

Abbreviation: dy/dx, marginal effect in the increase of x over y; NSAID, nonsteroidal anti-inflammatory drug.

^a $P=$.005.

^b $P<$.001.

^c $P=$.036.

rate of cardiovascular symptoms (16.6%). The frequency of cardiovascular symptoms in anaphylaxis episodes due to general anesthetics was 37.6% (Table 5).

On analyzing the most severe reactions (those in which there was involvement of 3 or more systems), there were no significant differences for atopy, age, number of episodes, severity of reaction, or involvement of NSAIDs, β -lactam antibiotics, or general anesthetics.

Discussion

It is difficult to compare results among epidemiological studies of anaphylaxis primarily because of differences in study populations, diagnostic criteria, and notification methodology. There is also a paucity of epidemiological studies focusing on drug-induced anaphylaxis only.

In our study, the prior standardization of international diagnostic criteria in drug-induced anaphylaxis applied by allergology and clinical immunology specialists allowed a more uniform methodology.

Similarly to other authors, we found more cases of drug-induced anaphylaxis in adults and females, and also a predominance of males in cases seen in children under 18 years of age [9,10].

The lower rate of hypersensitivity reactions to drugs seen in children and adolescents (8%) can be partly explained by lower exposure and differences in mechanisms of immunological response. Rubio et al [17] found a 1.5-increased risk of hypersensitivity reactions to drugs in adults compared with children, but similar rates of anaphylaxis in the 2 age groups.

NSAIDs were the main cause of drug-induced anaphylaxis in our series, coinciding with reports from other outpatient studies [6,18-20] but also contrasting with findings by Cianferoni et al [10], who reported that NSAIDs were the second most common cause, after antibiotics.

The estimated risk of penicillin-induced anaphylaxis among the general population in the United States is high, with ranges between 0.7% and 10% [21,22]. In our series, the number of cases of antibiotic-induced anaphylaxis in children was slightly higher than that of NSAID-induced anaphylaxis, and lower than that seen in other series [23,24].

It is generally agreed that preferential COX-1 inhibitors are the main type of NSAID involved in anaphylaxis. In our study, acetylsalicylic acid, diclofenac, and ibuprofen accounted for 88% of all such cases. In a study by Quiralte et al [25], naproxen, diclofenac, and ibuprofen were reported to carry a higher risk of anaphylactic reactions than other NSAIDs.

Pyrazoline derivatives, and metamizole in particular, are considered to be the main NSAIDs responsible for immediate-onset anaphylaxis [19]. In our population only 8.7% of NSAID-induced anaphylactic reactions were related to metamizole. We did not find a higher prevalence of atopy or more severe reactions in patients who reacted to metamizole compared with those who reacted to other NSAIDs, unlike Sanches-Borges et al [26], who reported that 69.2% of such patients were atopic and that 72.7% had more severe reactions.

Adverse reactions to selective or preferential COX-2 inhibitor NSAIDs and paracetamol are rare, and these drugs are considered an alternative in cases of anaphylaxis to preferential COX-1 inhibitors [19,25]. Their increased use may explain the number of anaphylaxis cases related to nimesulide, selective COX-2 inhibitors, and paracetamol, which in our series accounted for 6% of all NSAID-induced episodes.

Some authors have found that NSAID-anaphylactic reactions are mainly specific to a particular drug or group of drugs [25,26]. In our study, however, a majority of patients (62%) had recurrent anaphylaxis to NSAIDs from distinct pharmacological groups, suggesting that a specific immunological mechanism is unlikely. Diclofenac was associated with a surprisingly high number of cases of recurrence to the same NSAID. However, unlike Asero et al [27], we did not have information on acetylsalicylic acid challenge tests to define cases of selective hypersensitivity to a single NSAID.

In agreement with previous reports, we found a higher rate of anaphylaxis to β -lactam antibiotics (81.1%) than to non- β -lactam antibiotics, which are rarely implicated in anaphylaxis [3]. There was a high rate of anaphylaxis to β -lactam penicillins (60.4%), and more cases due to aminopenicillins and cephalosporins than to benzylpenicillins; in this respect our results are similar to those seen by Blanca Gomez et al [28]. In our population, cefazolin was responsible for anaphylaxis in 56.5% of patients allergic to cephalosporins. This high number of cases might be due to the frequent use of this antibiotic in Portugal, particularly as prophylaxis in surgical protocols. Changes in β -lactam prescription patterns in Europe may explain the increase in anaphylactic reactions to amoxicillin and cephalosporins and the decrease in penicillin-related cases in recent years, although few epidemiological studies have provided supporting data [28].

We highlight the high proportion of anaphylaxis cases induced by quinolone (11.7%). Similar rates were reported by Moneret-Vautrin et al [13] and may reflect the increasing use of quinolone antibiotics in the last decade.

Specialized studies in different countries have shown that NMBAs are a leading cause of intraoperative anaphylaxis [10,29]. In our series, they were the third most common cause of anaphylaxis. In a study by Faria et al [30] NMBAs were identified as inducers of anaphylaxis in 62.5% of cases, and the authors highlighted the high rate of moderate and severe episodes.

Severe reactions attributed to ICM have decreased with the reduction in use of high-osmolarity ionic formulations. In a European study carried out by Brockow et al [31] in 220 patients with a hypersensitivity reaction to ICM, 8.5% had grade II or III anaphylaxis [31]. We observed a low rate of anaphylaxis to ICM in our population (0.96%).

Of the remaining drug groups, anaphylactic reactions to systemic corticosteroids and cytostatics, particularly platinum-based chemotherapeutic agents, were the most frequent. Because these are core drugs that are not always replaceable, desensitization must be considered in some cases.

No cases of anaphylaxis to new treatments such as biological modifiers and monoclonal antibodies were reported.

In 94% of our patients, the symptoms occurred within the first 2 hours. Interestingly, all 4 anaphylactic reactions that occurred between 2 and 8 hours were related to weak COX-1 inhibitors (nimesulide, paracetamol, and etoricoxib). This may be because there are non-immunological mechanisms at play that are not completely understood or because initial symptoms were misinterpreted or underestimated.

Mucocutaneous symptoms are common in anaphylaxis although the absence of these symptoms does not rule out anaphylaxis, and it is important to pay attention to other early extracutaneous symptoms in the clinical diagnosis [3]. In our series, mucocutaneous symptoms were observed in 7.8% of cases. On comparing the involvement of 3 or more systems between the 3 main drug groups (NSAIDs, β -lactams, and NMBAs), the risk of respiratory and mucocutaneous symptoms would appear to be higher in anaphylaxis due to NSAIDs, while that of cardiovascular symptoms would appear to be lower. By contrast, in the case of anaphylaxis induced by general anesthesia, there appears to be a higher risk of cardiovascular symptoms. Unlike Pumphrey et al [14], we did not find a high rate of cardiovascular collapse in elderly patients.

Atopy was not a significant risk factor for anaphylaxis in any of the 3 main drug groups; our findings in this respect are similar to those of other authors [3,18].

A high risk of anaphylaxis has been reported in individuals with asthma, and severe asthma has been associated with a high risk of fatal outcome [3,14]. Studies performed in the United Kingdom and the United States found a 5.3%-increased risk of drug anaphylaxis in asthmatics [32]. In our series, 18.8% of patients were asthmatics, and the majority had anaphylaxis to NSAIDs.

There are few studies on risk factors for recurrent drug anaphylaxis. The recurrence rate in our series was 25.6%, which is lower than rates seen in the 1980s and 1990s in the United States [20]. The rate of recurrence of NSAID-induced anaphylaxis was particularly high (>13.5%), possibly because the treating physician and/or the patient may have underestimated the severity of the initial episode, leading to a failure to identify the causal agent. This would have led to a high risk of subsequent administration of the same drug or another drug from the same pharmacological group, due to a lack of knowledge of cross-reactivity mechanisms among patients and even physicians.

In a recent Australian study, Mullins [18] found severe symptoms during the initial anaphylaxis episode to be a predictive factor of recurrence of anaphylaxis. We did not observe this to be the case in our study.

We did not evaluate the use of concomitant medication, the condition under treatment, or the circumstances in which the episode occurred. Accordingly, we were unable to evaluate co-factors that potentially amplify anaphylaxis [10].

Although anaphylaxis is potentially fatal, only a quarter of the patients with drug-induced anaphylaxis in our series were seen in an emergency department, and a third of these were admitted to hospital.

Epinephrine is the first-line life-saving treatment in anaphylactic reactions, with a proven association between increased mortality and increased refractory or biphasic anaphylaxis if administration is delayed or omitted [3,4]. Under half of the patients in our series were treated with epinephrine. This rate is similar to that reported by other studies [33], but lower than reported more recently by Brown et al (57%) [34] and Pumphrey (62%) [14].

There was a very low rate of prescription of epinephrine auto-injectors, but it was significantly higher in children and adolescents, particularly at younger ages. This may be because physicians are more concerned with preventing onset of anaphylaxis in children and adolescents than in adults. The underprescription of epinephrine auto-injectors in cases of anaphylaxis is well-known, and also holds for Portugal, as shown by Branco Ferreira et al [35].

In the case of drug-induced anaphylaxis, once the risk has been identified, prescribing epinephrine auto-injectors can be a matter of debate, particularly in cases of anaphylaxis to diagnostic or treatment agents used exclusively in hospitals, such as general anesthetic agents, cytostatics, or ICM. Epinephrine should be prescribed in cases of severe anaphylaxis because it can transmit a feeling of safety and minimize the fear of drug administration that is common in patients who have previously had a sense of imminent death.

Conclusions

Drugs are considered to be the main trigger of anaphylaxis, particularly in adults. Prescription patterns and genetic, environmental, or unidentified co-factors may influence the rate of drug-induced anaphylaxis in different populations. However, there seems to be consensus that NSAIDs, antibiotics, NMBAs, and cytostatics are the main drugs responsible for inducing anaphylaxis.

As anaphylaxis is unpredictable and potentially fatal, its recognition and prevention is vital. Early administration of epinephrine is of extreme importance as relapses are common. We highlight the need for urgent referral to an allergist for a correct diagnosis following the first episode. The allergist plays a vital role in the identification of the culprit drug, the recommendation of safe alternatives, and the transmission of information to the patient and his/her physician and health care team.

Acknowledgments

Alexandra Santos, Ana Célia Costa, Ana Mendes, Ana Morête, Ana Teresa Silva, Carlos Lozoya, Carlos Neto Braga, Cristina Santa Marta, Elisa Pedro, Eugénia Almeida, Fátima Duarte, Filipa Sousa, Graça Pires, Isabel Mascarenhas, José Geraldo Dias, Leonor Viegas, Luís Araújo, Margarida Cortez Castro, Miguel Paiva, Paula Leiria Pinto, Pedro Martins, Rui Silva, Sara Pereira da Silva, Susana Lopes da Silva, Teresa Moscoso for their contributions of case histories of drug-

induced anaphylaxis and to Ana Lopes of the Universidade Nova de Lisboa for the statistical analysis.

Funding

The authors declare that no funding was received for the present study.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

Previous Presentation

This study was presented in poster form at the Drug Hypersensitivity Meeting, DHM5, in Munich in April 2012.

References

1. Wester K, Jonsson AK, Spigset O, Druid H, Hagg S. Incidence of fatal adverse drug reactions: a population based study. *Br J Clin Pharmacol.* 2007;65:573-9.
2. Ring J, Messmer K. Incidence and severity of anaphylactoid reactions to colloid volume substitutes. *Lancet.* 1977;1:466-9.
3. Lieberman P, Nicklas RA, Oppenheimer J, Kemp SF, Lang DM, Bernstein DI, Bernstein JA, Burks AW, Feldweg AM, Fink JN, Greenberger PA, Golden DB, James JM, Kemp SF, Ledford DK, Lieberman P, Sheffer AL, Bernstein DI, Blessing-Moore J, Cox L, Khan DA, Lang D, Nicklas RA, Oppenheimer J, Portnoy JM, Randolph C, Schuller DE, Spector SL, Tilles S, Wallace D. The diagnosis and management of anaphylaxis practice parameter 2010 Update. *J Allergy Clin Immunol.* 2010;126:477-80.
4. Simons FE, Arduzzo LR, Bilò MB, Dimov V, Ebisawa M, El-Gamal YM, Ledford DK, Lockey RF, Ring J, Sanchez-Borges M, Senna GE, Sheikh A, Thong BY, Worm M; World Allergy Organization. 2012 Update: World Allergy Organization Guidelines for the assessment and management of anaphylaxis. *Curr Opin Allergy Clin Immunol.* 2012;12(4):389-99.
5. Peng MM, Jick H. A population-based study of the incidence, cause, and severity of anaphylaxis in the United Kingdom. *Arch Intern Med.* 2004;164:317-9.
6. Sole D, Ivancevich JC, Borges MS, Coelho MA, Rosario NA, Arduzzo LR, Bernd LA; Latin American Anaphylaxis Working Group. Anaphylaxis in Latin America: a report of the online Latin American survey on anaphylaxis (OLASA). *Clinics (Sao Paulo).* 2011;66(6):943-7.
7. Botelho C, Cruz L, Rodrigues J, Castel-Branco MG. Anaphylaxis in a central Portuguese hospital - A 10 years overview. *Rev Port Imunoalergologia.* 2008;16:57-71.
8. Morais-Almeida M, Gaspar A, Santa-Marta C, Piedade S, Leiria-Pinto P, Pires G, Rosado-Pinto J. Anaphylaxis: from notification and knowledge to management. *Rev Port Imunoalergologia.* 2007;15:19-41.
9. Silva R, Gomes E, Cunha L, Falcão H. Anaphylaxis in children: A nine years retrospective study (2001—2009). *Allergol Immunopathol (Madr).* 2012 Jan-Feb;40(1):31-6.
10. Thong BY, Tan TC. Epidemiology and risk factors for drug allergy. *Br J Clin Pharmacol.* 2011;71:684-700.
11. Cianferoni A, Novembre E, Mugnaini L, Lombardi E, Bernardini R, Pucci N, Vierucci A. Clinical features of acute anaphylaxis

- in patients admitted to a university hospital: an 11-year retrospective review (1985–1996). *Ann Allergy Asthma Immunol.* 2001;87:27-32.
12. International Collaborative Study of Severe Anaphylaxis. Risk of anaphylaxis in a hospital population in relation to the use of various drugs: an international study. *Pharmacoepidemiol Drug Saf.* 2003;12:195-202.
 13. Moneret-Vautrin DA, Morisset M, Flabbee J, Beaudouin E, Kanny G. Epidemiology of life-threatening and lethal anaphylaxis: a review. *Allergy.* 2005;60:443-51.
 14. Pumphrey R. Anaphylaxis: can we tell who is at risk of a fatal reaction? *Curr Opin Allergy Clin Immunol.* 2004;4:285-90.
 15. Ribeiro-Vaz I, Marques J, Demoly P, Polónia J, Gomes ER. Drug-induced anaphylaxis: a decade review of reporting to the Portuguese Pharmacovigilance Authority *Eur J Clin Pharmacol.* 2013;69(3):673-81.
 16. Romano A, Torres MJ, Castells M, Sanz ML, Blanca M. Diagnosis and management of drug hypersensitivity reactions. *J Allergy Clin Immunol.* 2011;127(3 Suppl):S67-73.
 17. Rubio M, Bousquet PJ, Gomes E, Romano A, Demoly P. Results of drug hypersensitivity evaluations in a large group of children and adults. *Clin Exp Allergy.* 2012;42:123-30.
 18. Mullins RJ. Anaphylaxis: risk factors for recurrence. *Clin Exp Allergy.* 2003; 33:1033-40.
 19. Kowalski ML, Makowska JS, Blanca M, Bavbek S, Bochenek G, Bousquet J, Bousquet P, Celik G, Demoly P, Gomes ER, Niżankowska-Mogilnicka E, Romano A, Sanchez-Borges M, Sanz M, Torres MJ, De Weck A, Szczeklik A, Brockow K. Hypersensitivity to nonsteroidal anti-inflammatory drugs (NSAIDs) - classification, diagnosis and management: review of the EAACI/ENDA and GA2LEN/HANNA. *Allergy.* 2011;66:818-29.
 20. Kemp SF, Lockey RF, Wolf BL, Lieberman P. Anaphylaxis. A review of 266 cases. *Arch Intern Med.* 1995;155:1749-54.
 21. Gomes ER, Demoly P. Epidemiology of hypersensitivity drug reactions. *Curr Opin Allergy Clin Immunol.* 2005;5:309-16.
 22. Neugut AI, Ghatak AT, Miller RL. Anaphylaxis in the United States: an investigation into its epidemiology. *Arch Intern Med.* 2001;161:15-21.
 23. Braganza SC, Acworth JP, Mckinnon DR, Peake JE, Brown AF. Paediatric emergency department anaphylaxis: different patterns from adults. *Arch Dis Child.* 2006;91:159-63.
 24. Gamboa PM. The epidemiology of drug allergy-related consultations in Spanish Allergology services: *Alergológica-2005.* *J Investig Allergol Clin Immunol.* 2009;19(Suppl 2):45-50.
 25. Quiralte J, Blanco C, Delgado J, Ortega N, Alcntára M, Castillo R, Anguita JL, Sáenz de San Pedro B, Carrillo T. Challenge based clinical patterns of 223 Spanish patients with nonsteroidal anti-inflammatory-drug-induced-reactions. *J Investig Allergol Clin Immunol.* 2007;17:182-8.
 26. Sanchez-Borges M, Capriles-Hulett A. Atopy is a risk factor for non-steroidal anti-inflammatory drug sensitivity. *Ann Allergy Asthma Immunol.* 2000;84:101-6.
 27. Asero R. Oral aspirin challenges in patients with a history of intolerance to single non-steroidal anti-inflammatory drugs. *Clin Exp Allergy.* 2005;35:713-6.
 28. Gomez MB, Torres MJ, Mayorga C, Perez-Inestrosa E, Suaui R, Montañez MI, Juarez C. Immediate allergic reactions to betalactams: facts and controversies. *Curr Opin Allergy Clin Immunol.* 2004; 4:261-6.
 29. Mertes PM, Alla F, Tréchet P, Auroy Y, Jouglu E; Groupe d'Etudes des Réactions Anaphylactoïdes Peranesthésiques. Anaphylaxis during anesthesia in France: an 8-year national survey. *J Allergy Clin Immunol.* 2011;128:366-73.
 30. Faria E, Sousa N, Galdes L, Santos A, Chieira C. Peri-operative anaphylaxis in Coimbra: the experience of our drug allergy clinic. *Rev Port Imunoalergologia.* 2008;16:73-92.
 31. Brockow K, Romano A, Aberer W, Bircher AJ, Barbaud A, Bonadonna P, Faria E, Kanny G, Lerch M, Pichler WJ, Ring J, Rodrigues Cernadas J, Tomaz E, Demoly P, Christiansen C; European Network of Drug Allergy and the EAACI interest group on drug hypersensitivity. Skin testing in patients with hypersensitivity reactions to iodinated contrast media - a European multicenter study. *Allergy.* 2009;64:234-41.
 32. Koplin JJ, Martin PE, Allen KJ. An update on epidemiology of anaphylaxis in children and adults. *Curr Opin Allergy Clin Immunol.* 2011;11:492-6.
 33. Stewart AG, Ewan PW. The incidence, aetiology and management of anaphylaxis presenting to an accident and emergency department. *QJM.* 1996;89:859-64.
 34. Brown AF, McKinnon D, Chu K. Emergency department anaphylaxis: A review of 142 patients in a single year. *J Allergy Clin Immunol.* 2001;108:861-6.
 35. Ferreira MB, Alves RR. Are general practitioners alert to anaphylaxis diagnosis and treatment? *Eur Ann Allergy Clin Immunol.* 2006;38:83-6.
- *Manuscript received February 21, 2013; accepted for publication, April 30, 2013.*
- **Emília Maria Antunes Gomes de Faria**
- Serviço de Imunoalergologia
Hospitais da Universidade de Coimbra
Centro Hospitalar e Universitário de Coimbra
Praceta Prof. Mota Pinto
3000-075 Coimbra, Portugal
E-mail: emiliamfaria@hotmail.com