Eur J Clin Pharmacol (2013) 69:673–681
DOI 10.1007/s00228-012-1376-5

PHARMACOEPIDEMIOLOGY AND PRESCRIPTION

Drug-induced anaphylaxis: a decade review of reporting to the Portuguese Pharmacovigilance Authority

Inês Ribeiro-Vaz · Joana Marques · Pascal Demoly · Jorge Polónia · Eva Rebelo Gomes

Received: 23 March 2012 / Accepted: 6 August 2012 / Published online: 23 August 2012

Abstract
Purpose Anaphylaxis is a potentially fatal systemic adverse drug reaction (ADR). It is an unpredictable and mostly dose-independent event that occurs suddenly following exposure to the causative drug. Our objective was to characterize a case series of anaphylactic reactions reported to the Portuguese Pharmacovigilance authority during the past decade. Patients' demographic data and implicated drugs were analyzed as well as the severity of the ADR and time trends.
Methods This study was a retrospective analysis of episodes of anaphylaxis, defined according to the Second Symposium on the Definition and Management of Anaphylaxis Criteria, reported to the Portuguese Pharmacovigilance System between 1 January 2000 and 1 November 2010
Results Amongst the 16,157 ADR reported to the Portuguese Pharmacovigilance System during the 10-year study period, we found 918 (6 %) cases of anaphylaxis that met the proposed criteria. The age of the patients varied from 7 days to 91 years, with 87 cases (9 %) of anaphylaxis involving patients under 18 years of age. There was an overall female predominance (67 %), but the majority of pediatric patients were male (56 %). There was a trend toward increased reporting as the decade progressed, and 31 % (284) of all anaphylaxis cases were reported during the last 2 years of the study period. Of the anaphylaxis episodes reported, 19 % led to hospitalization and 24 (3 %) had a fatal outcome. Antibiotics were responsible for most cases (17 %) followed by nonsteroidal anti-inflammatory drugs/acetaminophen (13 %), antineoplastic/cytotoxic drugs and immune-modulators. Vaccines and radiographic contrast media were also important contributors to an anaphylactic event.
Conclusions In this series of drug-related anaphylaxis, we found that most of the reported episodes were associated with widely used drugs, such as antibiotics and analgesics. Anaphylaxis can occur at any age. The female gender was more highly represented, with the exception of pediatric patients.

Keywords Anaphylaxis · Drug-induced anaphylaxis · Pharmacovigilance · Adverse drug reaction reporting system

I. Ribeiro-Vaz (✉) · J. Marques · J. Polónia
Northern Pharmacovigilance Centre, Faculty of Medicine,
University of Porto,
Rua Doutor Plácido da Costa,
4200-450 Porto, Portugal
e-mail: inesribeirovaz@gmail.com

I. Ribeiro-Vaz
e-mail: inesvaz@med.up.pt

I. Ribeiro-Vaz · J. Marques
Faculty of Medicine of the University of Porto,
CINTESIS—Center for Research in Health
Technologies and Information Systems,
Porto, Portugal

P. Demoly
Allergy Unit, Département de Pneumologie,
Hôpital Arnaud de Villeneuve,
Montpellier, France

P. Demoly
Inserm U657, University Hospital of Montpellier,
Montpellier, France

E. R. Gomes
ImmunoAlergology Department, Porto Hospitalar Centre,
Porto, Portugal

Introduction

Anaphylaxis is usually defined as an acute systemic allergic reaction that results from the release of pharmacologically active mediators from activated mast cells and basophils. A specific immune-mediated reaction is not always documented, and such cases, formerly designated as anaphylactoid reactions, are now classified as non-allergic anaphylaxis

[1]. The severity of the reaction can vary from mild to life-threatening and can be rapidly progressive. Anaphylaxis is also a rare but potentially fatal adverse drug reaction (ADR), classified as a type-B reaction as it is mostly an unpredictable and dose-independent event that occurs suddenly after the patient comes into contact with the causative drug [2].

Data on the incidence of drug-induced anaphylaxis are limited. There are a small number of published studies on this subject, but most refer to specific drugs or special patient conditions [3–6]. Our literature search revealed interesting data on hospital admissions related to drug-induced anaphylaxis [7] and a few case series studies [8, 9], of which the Van Der Klauw study [10] is one of the most extensive. This latter study from The Netherlands includes 936 cases of drug-induced anaphylaxis. Based on their findings, the authors concluded that the drugs most frequently associated with anaphylaxis leading to admission were glafenine, nonsteroidal anti-inflammatory drugs (NSAIDs) and antibiotics; they also detected a female predominance (65 %).

Here, we present an analysis of 918 reports of drug-induced anaphylaxis received by the National Pharmacovigilance System of the Portuguese Medicines Authority (INFARMED) from 2000 to 2010.

Materials and methods

In Portugal, the National Pharmacovigilance System was created in 1992 as a centrally administered organization. In 2000, regional centers were created to collect spontaneous ADR reports from healthcare professionals of each region. These reports are voluntary and are made mostly by physicians, pharmacists, nurses and technical staff. They are mostly collected on a standardized form that includes information on patient demographics, ADR description, drugs involved and clinical and pharmacological history. The reports can also be made by telephone or e-mail (non-structured forms).

In this study, we collected not only the reports made by healthcare professionals, but also the ones made by marketing authorization holders. We analyzed those reports received from 1 January 2000 to 1 November 2010 that met the criteria of anaphylaxis proposed by the Second Symposium on the Definition and Management of Anaphylaxis [11]. According to this definition, anaphylaxis is a serious systemic reaction fulfilling at least one of the following three clinical criteria:

- Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue or both (e.g. generalized hives, pruritus or flushing, swollen lips/tongue/uvula) and, at least, one of the following:
  a. Respiratory compromise (e.g. dyspnoea, wheezing-bronchospasm, stridor, reduced peak expiratory flow, hypoxemia)
  b. Reduced blood pressure or associated symptoms of end-organ dysfunction (e.g. hypotonia, collapse, syncope, incontinence)
- Occurrence of two or more of the following, which occur rapidly after exposure to a likely allergen for that patient (minutes to several hours):
  a. Involvement of the skin–mucosal tissues (e.g. generalized hives, itch-flush, swollen lips/tongue/uvula)
  b. Respiratory compromise (e.g. dyspnoea, wheeze-bronchospasm, stridor, reduced peak expiratory flow, hypoxemia)
  c. Reduced blood pressure or associated symptoms (e.g. hypotonia, collapse, syncope, incontinence)
  d. Persistent gastrointestinal symptoms (e.g. abdominal pain with cramps, vomiting)
- Reduced blood pressure after exposure to a known allergen for that patient (minutes to several hours):
  a. Infants and children: low systolic blood pressure (age specific) or a >30 % drop in systolic blood pressure.
  b. Adults: systolic blood pressure of <90 mmHg or >30 % decreased from that person's baseline.

We started by collecting all of the reports on the 16,157 cases of ADR declared to the INFARMED in which at least one of the terms included in the anaphylaxis definition described above was mentioned as an ADR. Based on this analysis, we identified2,965 cases. After all duplicate case reports were eliminated and the anaphylaxis criteria applied, the number fell to 2,013 cases. We then analyzed each narrative (which is a brief description of the episode made by the reporter) in more detail in order to understand whether or not it could be considered an anaphylactic reaction. There were several reports that met our research criteria in terms of an ADR, such as pruritus and vomiting, but the temporal relationship was inconsistent. The temporal relationship was considered characteristic of anaphylaxis if the reaction occurred within few hours after exposure to the causative drug, or was described as "minutes,, "hours," "shortly" or "immediately" after exposure.

This analysis finally led us to 918 reported cases of what was considered to be a plausible diagnosis of anaphylaxis (see Fig. 1.)

The Medical Dictionary for Regulatory Activities (MedDRA®) was used to group adverse reactions, and the nomenclature used for drug class classification was that adopted by Portuguese Authority of Medicines and Health Products (INFARMED, IP) and published in national legislation [12]. This classification includes 19 pharmacotherapeutic groups; within each group there are several subgroups (this number varies from 2 to 13 subgroups).

We used the international guidelines, which are also the ones adopted by the Portuguese System of Pharmacovigilance, to

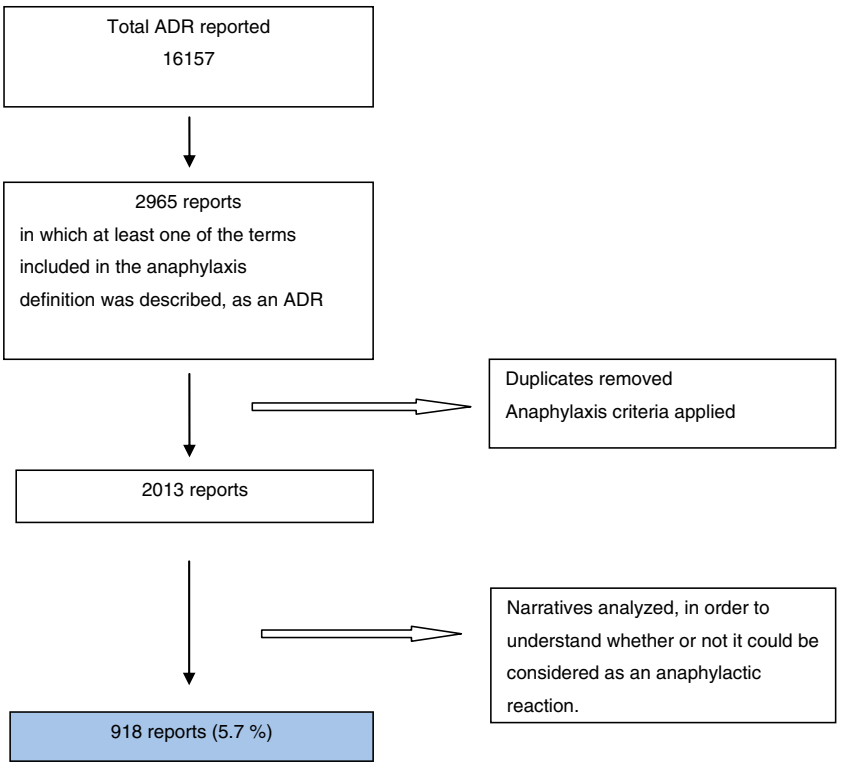

Fig. 1 Flowchart of case selection. *ADR* Adverse drug reaction

assess the seriousness of the episodes. According to these criteria, a serious adverse event or reaction is any untoward medical occurrence that fulfills at least one of the following criteria: (1) results in death; (2) requires inpatient hospitalization or prolongation of existing hospitalization; (3) results in persistent or significant disability/incapacity; (4) is life-threatening [13].

We analyzed the case reports for a causal relationship between exposure and anaphylaxis in accordance with the criteria adopted by Portuguese Pharmacovigilance System. All spontaneous ADR reports entered in the System are classified according to the World Health Organization (WHO) system for standardized causality assessment [13] in order to produce a consistent quantitative estimation of relationship likelihood. According to this method, reported cases are classified as *certain* (the higher causality degree), *probable*, *possible*, *unlikely*, *conditional* or *unclassifiable*. The assessment criteria include: time relationship to drug intake, pharmacological or phenomenological plausibility, concomitant disease or drugs, plausibility of withdrawal response and rechallenge data (when available). In this study, we also analyzed our cases according to this classification.

The total number of ADR reports was compared with the anaphylaxis reported using the Pearson chi-square statistical test. A Poisson regression was applied in order to analyze the reporting time trend.

Results

During the decade study, we found 918 reported cases of ADR that met the reference criteria and were considered to be anaphylaxis after review. Based on the Portuguese census, this equates, on average, to 7.9 reported cases per million of inhabitants per year. However, it is important to note that theoretically the same patient can be represented by more than one episode and because of the anonymity of the Pharmacovigilance System, it is not possible to access this information.

Reporting trend

There was a trend toward increased reporting as the decade progress, and 31 % (284) of the cases were reported during the last 2 years of the study period (2009–2010), as seen in Table 1. In the reference period, Poisson regression models, adjusted to variations in the Portuguese population, showed evidence of an increasing trend in the number of cases of anaphylaxis reported ($p<0.001$).

However, based on a comparison with the total number of ADR reports in the decade studied, we concluded that the cases of anaphylaxis reported represent about 5–7 % of the reports with no significant variation over the years analyzed ($p=0.232$). This proportion is graphically represented in Fig. 2.

Table 1 Variation in the number of anaphylaxis cases reported annually

Year	Reported cases of anaphylaxis, *n* (%)	Reported number of anaphylaxis cases/million of inhabitants[a]
2000	28 (3)	2.7
2001	61 (7)	5.9
2002	49 (5)	4.7
2003	63 (7)	6.0
2004	95 (10)	9.0
2005	71 (8)	6.7
2006	73 (8)	6.9
2007	86 (9)	8.1
2008	108 (12)	10.2
2009	149 (16)	14.0
2010	135 (15)	12.7
Total	918	7.9/year

[a] Source: National Statistics Institute: www.ine.pt

Demographics

The age of the patients at the time of the ADR episode varied from 7 days to 91 years [mean 48 years, standard deviation (SD) 21 years]. Eighty-seven (9 %) patients were aged 18 years or younger at the time of their ADR episode.

There was an overall female predominance (67 %) in the ADR reports. Among adults, 70 % of the ADR involved women. In contrast, among the pediatric population, there was a male predominance (56 %). These values were significantly different ($p<0.001$).

Drugs involved

Antibiotics formed the pharmacotherapeutic group responsible for most of the reported reactions (17 %) followed by NSAIDs/acetaminophen (13 %), cytotoxic drugs (12 %) and immune-modulators (9 %); this latter group showed an important increase in the last 3 study years. Vaccines and radiographic contrast media were also important contributors to ADR, with 60 (7 %) and 40 (4 %) reports, respectively (Table 2)

Seriousness and causality assessment

According to the WHO system for standardized case causality assessment [13], 388 (42 %) of the included reports were classified as probable, 77 (8 %) as possible and only 35 (4 %) as certain. Among the 918 accepted cases, 819 (89 %) were considered as serious, 19 % of the episodes led to hospitalization, and 24 (3 %) were fatal. Of these fatalities, four were due to antibiotics, four to antineoplastic drugs and three to NSAIDs/paracetamol. Table 3 describes the drugs involved as well as the causality attributed to each reported fatality.

The outcome in 741 cases (81 %) was a complete recovery, while recovery was characterized by a number of sequels in nine cases. There were 24 cases of a fatal outcome. For all the other episodes (13 %), the outcome is unknown.

Pediatric population

A subgroup analysis was conducted in children. There were 87 reported cases that concerned a pediatric patient (age ≤18 years). As in the whole population, there was a trend toward increased reporting of anaphylaxis as the decade progressed, but the variation was not statistically significant ($p=0.615$). Based on a comparison with the total number of reported ADR in children, we concluded that the cases of reported anaphylaxis represent about 4–10 % of the total, again with no significant variation over the years analyzed ($p=0.277$). This is graphically presented in Fig. 3. The

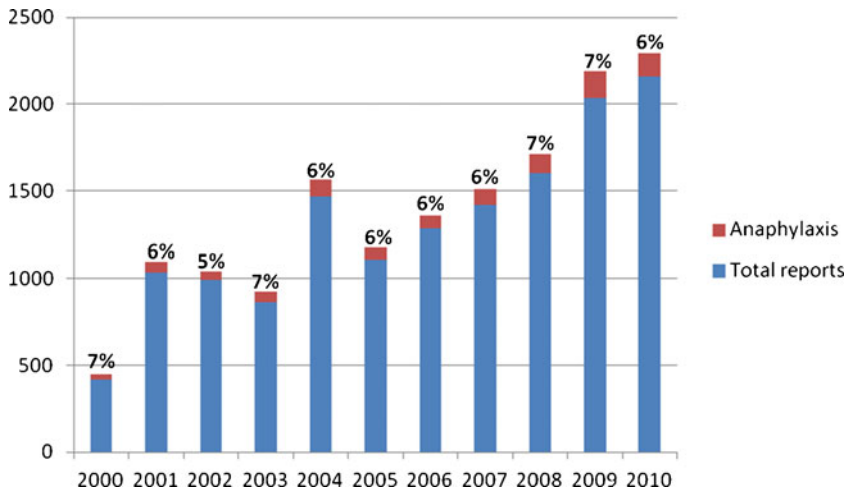

Fig. 2 Proportion of anaphylaxis cases among the total number of ADR reports

Table 2 Pharmacotherapeutic groups and subgroups involved in reports of anaphylaxis

Drug classification		
Pharmacotherapeutic group	Pharmacotherapeutic subgroup	Anaphylaxis reported cases, *n* (%)
Anti-infectious	Antibiotics	153 (16.7)
	Antifungals	1 (0.1)
	Antivirals	10 (1.1)
	Anthelmintics	3 (0.3)
Central nervous system	General anesthetics	3 (0.3)
	Analgesics and antipyretics[a]	3 (0.3)
	Opioid analgesics	10 (1.1)
	Other drugs acting on CNS	3 (0.3)
	Local anesthetics	8 (0.9)
	Neuromuscular blockers	9 (1.0)
	Antiparkinson agents	4 (0.4)
	Anticonvulsants and antiepileptics	14 (1.5)
	Antiemetic and anti-vertigo agents	4 (0.4)
	Psycholeptics+ psychoanaleptics	21 (2.3)
Cardiovascular system	Antidysrhythmics	17 (1.9)
	Antihypertensives	23 (2.5)
	Vasodilators	3 (0.3)
	Lipid-lowering agents	7 (0.8)
Blood	Antianemics	14 (1.5)
	Hematopoietic growth factors	7 (0.8)
	Anticoagulants and antiplatelet agents	11 (1.2)
	Antifibrinolytic agents and hemostatics	4 (0.4)
Respiratory system	Antiasthmatic and bronchodilators	8 (0.9)
	Antitussives and expectorants	8 (0.9)
Gastrointestinal system	Drugs acting on the mouth and oropharynx	1 (0.1)
	Antacids and antiulcerous	12 (1.3)
	Gastrointestinal motility modifiers	2 (0.2)
	Antispasmodics	1 (0.1)
	Enzymes	2 (0.2)
Genitourinary system	Urinary anti-infectives and antiseptics	4 (0.4)
	Other drugs used in genitourinary disorders	7 (0.8)
Hormones and drugs used to treat endocrine diseases	Hypothalamic and pituitary hormones, analogs and antagonists	3 (0.3)
	Corticosteroids	10 (1.1)
	Insulins, oral antidiabetics and glucagon	1 (0.1)
	Sex hormones	1 (0.1)
Locomotor system	NSAIDs and paracetamol	123 (13.4)
	Drugs used to treat gout	3 (0.3)
	Anti-inflammatory enzymes	1 (0.1)
	Bone and calcium metabolism modifiers	11 (1.2)
Anti-allergic medication	Antihistaminics	5 (0.5)
Nutrition	Vitamins and minerals	1 (0.1)
Corrective agents in blood volume and electrolyte disturbances	Plasma substitutes	6 (0.7)
Drugs for skin disorders	Anti-infective, skin application	3 (0.3)
	Keratolytics and antipsoriatics	1 (0.1)
	Other drug used in dermatology	1 (0.1)
Drugs used in otorhinolaryngological disorders	Nasal application products	2 (0.2)
Drugs for eye disorders	Drugs used to treat glaucoma	1 (0.1)
	Other drugs and products used in ophthalmology	5 (0.5)
Antineoplastic drugs and immune-modulators	Cytotoxic drugs	113 (12.3)
	Hormones and anti-hormones	8 (0.9)
	Immune-modulators	85 (9.3)
Drugs used to treat poisoning	Drugs used to treat poisoning	6 (0.6)
Vaccines and immunoglobulins	Vaccines	60 (6.5)
	Immunoglobulins	7 (0.8)
Diagnosis media	Radiographic contrast media	40 (4.4)
	Contrast media for NMR imaging	7 (0.8)
Others	Associations[b]	34 (3.7)
	Other products[c]	3 (0.3)
Total		918

NSAIDs, Nonsteroidal anti-inflammatory drugs; CNS, central nervous system; NMR, neutron magnetic imaging

[a] This subgroup includes drugs with analgesic and/or antipyretic effects which do not interfere with the opioid receptors and for whom anti-inflammatory activity is not the main drug effect. NSAIDs are not included in this group. The three cases reported refer to clonixine

[b] Associations were defined as those cases in which more than one drug was suspected to cause the anaphylaxis, and the drugs belonged to different pharmacotherapeutic groups

[c] One of these three cases was caused by an immunotherapy extract (classified as "other products", according to the nomenclature used)

proportion of anaphylaxis reports among children was found to be similar to that found analyzing the entire population.

The age of the pediatric patients varied from 7 days to 18 years (mean 9 years; SD 5 years) and there was a male predominance (56 %). Most of the cases reported in the pediatric population (37 %) were attributed to exposure to vaccines and immunoglobulins, followed by exposure to antibiotics (22 %) and NSAIDs/paracetamol (7 %).

Table 3 Description of the fatal episodes

Class of suspected drug	Causality term				Total
	Probable	Possible	Unclassifiable	(Unknown)	
Antibiotics	2	0	0	2	4
Antiepileptics and anticonvulsants	0	0	0	2	2
Antiarrhythmics	0	0	0	1	1
Antianemics	1	0	0	0	1
Hematopoietic growth factors	0	0	0	2	2
NSAIDs and paracetamol	2	0	0	1	3
Antibacterials, topical	0	1	0	0	1
Antineoplastic drugs	2	1	0	1	4
Immunomodulators	0	0	0	1	1
Cytoprotective agents	0	1	1	0	2
Contrast media	0	1	0	0	1
Associations	1	1	0	0	2
Total	8	5	1	10	24

In terms of seriousness, 75 (86 %) cases were considered to be serious, and 22 % led to hospitalization. No fatalities related to the ADR were reported.

The outcome of 78 (90 %) of these cases was complete recovery. One child died but the death was not related to the ADR and the outcome was unknown for the remaining eight cases.

Discussion

Worldwide, reported annual incidences of anaphylaxis range from 3.2 to 49.8 cases per 100,000 general population, and the number appears to be increasing in recent years [14–18]. Drugs are the major triggers reported in most studies [7, 17, 19], and drug-induced anaphylaxis death appears to be increasing, in contrast to anaphylaxis death due to other causes [18].

We found an overall incidence of 7.9 reported cases per million Portuguese inhabitants (0.79 cases per 100,000 population) during the study period, but this number is just those cases related to drug-induced anaphylaxis. Taking into consideration that the published data show that only 5–10 % of the cases are actually reported to pharmacovigilance systems [20–24]—even when serious reactions are concerned, such as Stevens–Johnson syndrome [25] and anaphylaxis during anesthesia [26]—we suggest that our estimated numbers are similar to those previously described by other authors.

We found an increasing trend toward reporting cases of anaphylaxis in both adults and children as the study decade progressed. However, this trend is probably due to an overall increase in ADR reporting as the ratio between number of anaphylaxis-related reports and total number of ADR reports did not change significantly and, curiously, it was similar in the pediatric and the general population.

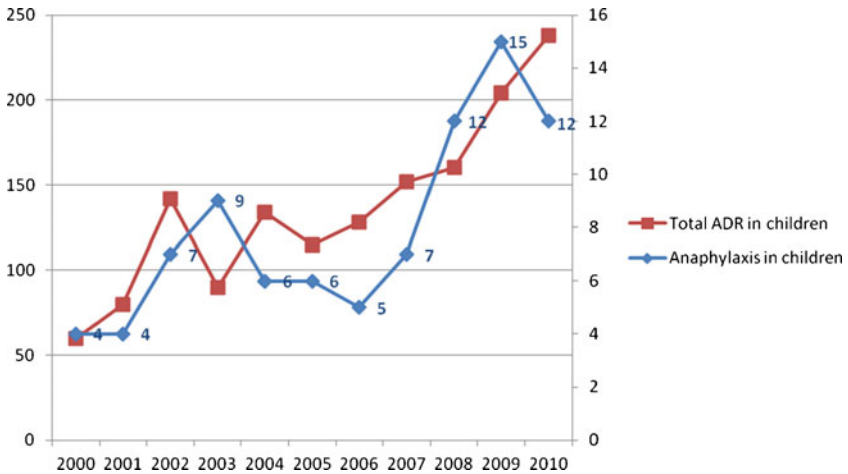

Fig. 3 Cases of anaphylaxis reported in children (≤18 years) compared with total cases of ADR reported in children

A female predominance is reported in most studies that assess ADR in general [27] and drug-induced anaphylaxis specifically [14, 19], and our data confirm this preponderance. In the pediatric subpopulation, however, we found a male predominance. The different behavior of the gender variable according to age has also been reported by other authors referring to ADR in general [27, 28] and to anaphylaxis specifically [14, 26, 29, 30].

Drug-induced anaphylaxis was predominantly associated with antibiotics and NSAID drugs, as reported in other studies on drug hypersensitivity reactions [7,19]. The other three main pharmacological groups we identified as contributors to anaphylaxis were antineoplastic/cytotoxic drugs, vaccines and radio contrast media; these groups have also been identified as important causes of ADR and hypersensitivity by other authors [10]. The increasing number of reports related to immune modulators—also reported in other studies [17]—is most probably explained by the raising clinical indications and use of these drugs over the last decade. According to the WHO system for standardized causality assessment [13], most of the included reports could be classified as probable and only 35 as certain. This distribution is similar to that found in other publications concerning ADR and drug-induced anaphylaxis [31]. However, these data should be carefully interpreted as the methods used by pharmacovigilance systems to assess causality seems to have a low positive predictive value compared to standard clinical evaluation, especially concerning drug hypersensitivity reactions [32, 33] .

The important proportion of cases considered to be serious is probably associated with reporting bias as serious reactions are more likely to be reported than less serious cases and because anaphylaxis is by definition a potentially fatal event.

In most of the reported cases the patient showed a fully recovery, but there were 24 fatalities due to anaphylaxis in the study period. In a study from New Zealand on cases of anaphylaxis with a fatal outcome that covered 20 years, the most common cause was found to be drugs [34]. Also, in a recent study from Australia on anaphylaxis-related fatality (obtained from a mandatory national mortality database), 112 cases were identified over 9 years, 62 of which were attributed to drugs (22 caused by drugs and 42 most likely caused by drugs); these numbers are not very different from those we found when the differences in populations is taken into account [18]. In fact, according to national census, the Portuguese population average in this decade was about 10.5 million inhabitants; in comparison, the Australian population average was about 20.3 million in the same period.

A total of 202 fatalities were reported in a 10-year review in the UK (passive reporting to a dedicated anaphylaxis deaths registry), with 88 of these attributed to drugs [35]. Also in the UK, an estimated prevalence of one anaphylaxis-related death annually per 3 million population [36, 37] was calculated, which would translate to three deaths annually based on the Portuguese general population of 10 million and 33 deaths over an 11-year period. Therefore, the numbers we found are within the expected range, even considering the referred underreporting problem.

Our results allow us to conclude that drug-induced anaphylaxis can occur at any age, but we do know that in children the most common trigger for anaphylaxis is food [29, 38–40]. Published data on drug-induced anaphylaxis in pediatric patients is scarce. In the 5-year retrospective review of Silva et al. [38], which involved 123 children presenting to the Emergency Department, only 6 % of the cases were associated with the use of drugs. In contrast, drugs were the identifiable cause in 11.8 % of the pediatric cases included in the Bohlke et al. study [29]. We also found a significant number of cases of drug-induced anaphylaxis in children. We found no reported fatalities in children (a non-significant difference with the adult population). The drugs involved in drug-induced anaphylaxis in children are somewhat different from those associated with adult cases, with most of the reactions in the former being attributed to vaccines, which are well-known causes of pediatric ADR, as previously reported [31, 41–43].

There are several limitations to our study. First, the effectiveness of the Portuguese Pharmacovigilance System, on which our study is based, is compromised by the problem of underreporting. This problem is not exclusively Portuguese and is a well-recognized difficulty in studies carried out in developed countries [25, 44]. It has been estimated that reported ADRs rarely exceed 10 % of the real total [20–24]. Consequently, based on available data, we can just speculate about the true incidence of drug-induced anaphylaxis. Another important question that can be raised about all studies on anaphylaxis, including our study, concerns the differences in the definitions of anaphylaxis that can be used. The lack of a general standard case definition can lead to an inconsistent diagnosis [45] and therefore reporting. In this work we applied the diagnostic criteria proposed by the Second Symposium on the Definition and Management of anaphylaxis [11], and we reviewed all of the information available on the reports in order to reduce this problem, but even doing so this limitation cannot be completely overcome because reports can be incomplete or contain erroneous information. Finally, we must note that the retrospective nature of this study also reduces its ability to obtain complete data on some of the reactions, leading to potential inadequate or incomplete documentation (missing data). One of the consequences of this is, for example, our incapacity to assess risk factors when considering those related to demographic data.

Conclusion

We present a fairly extensive case series of suspected drug-induced anaphylaxis reported to the Portuguese Pharmacovigilance Authority over one decade. The available data show

that drug-induced anaphylaxis is a problem affecting all age groups and that the majority of patients were female. Most of the reported cases were considered to be serious events and included 24 fatal cases. The majority of the reports were classified as probable according to WHO system for standardized causality assessment and were attributed to commonly used drugs, such as antibiotics and NSAIDs.

Acknowledgments The authors would like to thank the Portuguese Medicines Authority (INFARMED) for its collaboration in this study. The data presented in our work were provided by INFARMED, but were assessed without validation by INFARMED.

Conflict of interest statement The author and co-authors have no conflict of interest.

References

1. Johansson SGO, Bieber T, Dahl R, Friedmann PS, Lanier BQ, Lockey RF et al (2004) Revised nomenclature for allergy for global use: Report of the Nomenclature Review Committee of the World Allergy Organization, October 2003. J Allergy Clin Immun 113(5):832–836
2. Aronson JK, Ferner RE (2003) Joining the DoTS: new approach to classifying adverse drug reactions. Br Med J 327:1222–1225
3. Haque RA, Wagner A, Whisken JA, Nasser SM, Ewan PW (2010) Anaphylaxis to patent blue V: a case series and proposed diagnostic protocol. Allergy 65(3):396–400
4. Mulla ZD, Ebrahim MS, Gonzalez JL (2010) Anaphylaxis in the obstetric patient: analysis of a statewide hospital discharge database. Ann Allergy Asthma Immunol 104(1):55–59
5. International Collaborative Study of Severe Anaphylaxis (2003) Risk of anaphylaxis in a hospital population in relation to the use of various drugs: an international study. Pharmacoepidemiol Drug Saf12(3):195–202
6. Botsis T, Ball R (2011) Network analysis of possible anaphylaxis cases reported to the US vaccine adverse event reporting system after H1N1 influenza vaccine. Stud Health Technol Inf 169:564–568
7. Van der Klauw MM, Stricker BH, Herings RM, Cost WS, Valkenburg HA, Wilson JH (1993) A population based case-cohort study of drug-induced anaphylaxis. Br J Clin Pharmacol 35(4):400–408
8. Marguet C, Couderc L, Blanc T, Amar R, Leloet C, Feray D et al (1999) Anaphylaxis in children and adolescents: apropos of 44 patients aged 2 months to 15 years. Arch Pediatr 6[Suppl 1]:72S–78S
9. Techapornroong M, Akrawinthawong K, Cheungpasitporni W, Ruxrungtham K (2010) Anaphylaxis: a ten years inpatient retrospective study. Asian Pac J Allergy Immunol 28(4):262–269
10. VanDerKlauw MM, Wilson JHP, Stricker BHC (1996) Drug-associated anaphylaxis: 20 years of reporting in the Netherlands (1974–1994) and review of the literature. Clin Exp Allergy 26 (12):1355–1363
11. Sampson HA, Munoz-Furlong A, Campbell RL, Adkinson NF Jr, Bock SA, Branum A et al (2006) Second symposium on the definition and management of anaphylaxis: summary report–Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network symposium. J Allergy Clin Immunol 117(2):391–397
12. Ministry of Health (2004) Order no. 21844/2004
13. World Health Organization (2011). The Uppsala Monitoring Centre, Uppsala. Available at: http://www.who-umc.org/. Accessed 9 Feb 2011
14. Decker WW, Campbell RL, Manivannan V, Luke A, St Sauver JL, Weaver A et al (2008) The etiology and incidence of anaphylaxis in Rochester, Minnesota: a report from the Rochester Epidemiology Project. J Allergy Clin Immunol 122(6):1161–1165
15. Gupta R, Sheikh A, Strachan DP, Anderson HR (2007) Time trends in allergic disorders in the UK. Thorax 62(1):91–96
16. Tang ML, Osborne N, Allen K (2009) Epidemiology of anaphylaxis. Curr Opin Allergy Clin Immunol 9(4):351–356
17. Sheikh A, Alves B (2000) Hospital admissions for acute anaphylaxis: time trend study. Br Med J 320(7247):1441
18. Liew WK, Williamson E, Tang ML (2009) Anaphylaxis fatalities and admissions in Australia. J Allergy Clin Immunol 123(2):434–442
19. Gonzalez-Perez A, Aponte Z, Vidaurre CF, Rodriguez LA (2010) Anaphylaxis epidemiology in patients with and patients without asthma: a United Kingdom database review. J Allergy Clin Immunol 125(5):1098–1104 e1
20. Backstrom M, Mjorndal T, Dahlqvist R (2004) Under-reporting of serious adverse drug reactions in Sweden. Pharmacoepidemiol Drug Saf 13(7):483–487
21. Figueiras A, Herdeiro MT, Polonia J, Gestal-Otero JJ (2006) Influence of pharmacists' attitudes on adverse drug reaction reporting—A case-control study in Portugal. Drug Saf 29(4):331–340
22. Cullen DJ, Bates DW, Small SD, Cooper JB, Nemeskal AR, Leape LL (1995) The incident reporting system does not detect adverse drug events: a problem for quality improvement. Jt Comm J Qual Improv 21(10):541–548
23. Le J, Nguyen T, Law AV, Hodding J (2006) Adverse drug reactions among children over a 10-year period. Pediatrics 118(2):555–262
24. Jha AK, Kuperman GJ, Teich JM, Leape L, Shea B, Rittenberg E et al (1998) Identifying adverse drug events: development of a computer-based monitor and comparison with chart review and stimulated voluntary report. J Am Med Inform Assoc 5(3):305–314
25. Mittmann N, Knowles SR, Gomez M, Fish JS, Cartotto R, Shear NH (2004) Evaluation of the extent of under-reporting of serious adverse drug reactions: the case of toxic epidermal necrolysis. Drug Saf 27(7):477–487
26. Mertes PM, Alla F, Trechot P, Auroy Y, Jougla E (2011) Anaphylaxis during anesthesia in France: an 8-year national survey. J Allergy Clin Immunol 128(2):366–373
27. Thong BY, Tan TC (2011) Epidemiology and risk factors for drug allergy. Br J Clin Pharmacol 71(5):684–700
28. Star K, Noren GN, Nordin K, Edwards IR (2011) Suspected adverse drug reactions reported for children worldwide: an exploratory study using VigiBase. Drug Saf 34(5):415–428
29. Bohlke K, Davis RL, DeStefano F, Marcy SM, Braun MM, Thompson RS (2004) Epidemiology of anaphylaxis among children and adolescents enrolled in a health maintenance organization. J Allergy Clin Immunol 113(3):536–542
30. Simons FE, Peterson S, Black CD (2002) Epinephrine dispensing patterns for an out-of-hospital population: a novel approach to studying the epidemiology of anaphylaxis. J Allergy Clin Immunol 110(4):647–651
31. Martinez-Mir I, Garcia-Lopez M, Palop V, Ferrer JM, Rubio E, Morales-Olivas FJ (1999) A prospective study of adverse drug reactions in hospitalized children. Br J Clin Pharmacol 47(6):681–688
32. Benahmed S, Picot MC, Hillaire-Buys D, Blayac JP, Dujols P, Demoly P (2005) Comparison of pharmacovigilance algorithms in drug hypersensitivity reactions. Eur J Clin Pharmacol 61(7):537–541
33. Benahmed S, Picot MC, Dumas F, Demoly P (2005) Accuracy of a pharmacovigilance algorithm in diagnosing drug hypersensitivity reactions. Arch Intern Med 165(13):1500–1505
34. Low I, Stables S (2006) Anaphylactic deaths in Auckland, New Zealand: a review of coronial autopsies from 1985 to 2005. Pathology 38(4):328–332

35. Pumphrey R (2004) Anaphylaxis: can we tell who is at risk of a fatal reaction? Curr Opin Allergy Clin Immunol 4(4):285–290
36. Pumphrey RS (2000) Lessons for management of anaphylaxis from a study of fatal reactions. Clin Exp Allergy 30(8):1144–1150
37. Pumphrey RS (2004) Fatal anaphylaxis in the UK, 1992–2001. Novartis Found Symp 257:116–228, discussion 28–32, 57–60, 276–285
38. de Silva IL, Mehr SS, Tey D, Tang ML (2008) Paediatric anaphylaxis: a 5 year retrospective review. Allergy 63(8):1071–1076
39. Braganza SC, Acworth JP, McKinnon DR, Peake JE, Brown AF (2006) Paediatric emergency department anaphylaxis: different patterns from adults. Arch Dis Child 91(2):159–163
40. Alves B, Sheikh A (2001) Age specific aetiology of anaphylaxis. Arch Dis Child 85(4):348
41. Kimland E, Rane A, Ufer M, Panagiotidis G (2005) Paediatric adverse drug reactions reported in Sweden from 1987 to 2001. Pharmacoepidemiol Drug Saf 14(7):493–499
42. Aagaard L, Weber CB, Hansen EH (2010) Adverse drug reactions in the paediatric population in Denmark: a retrospective analysis of reports made to the Danish Medicines Agency from 1998 to 2007. Drug Saf 33(4):327–339
43. Hawcutt DB, Mainie P, Riordan A, Smyth RL, Pirmohamed M (2012) Reported paediatric adverse drug reactions in the UK 2000–2009. Br J Clin Pharmacol 73(3):437–446
44. Hazell L, Shakir SA (2006) Under-reporting of adverse drug reactions: a systematic review. Drug Saf 29(5):385–396
45. Erlewyn-Lajeunesse M, Dymond S, Slade I, Mansfield HL, Fish R, Jones O et al (2010) Diagnostic utility of two case definitions for anaphylaxis: a comparison using a retrospective case notes analysis in the UK. Drug Saf 33(1):57–64

Author contributions

Inês Ribeiro-Vaz was responsible for most of the data collection and validation and also performed the statistical analysis. Joana Marques collaborated in data collection and validation. Pascal Demoly and Jorge Polónia supervised the writing of the paper. Eva Gomes conceptualized the revision and performed most of the literature review.