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Self-reported drug allergy in a general adult Portuguese population

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Summary

Aim To estimate the prevalence of self-reported drug allergy in adults.

Methods Cross-sectional survey of a general adult population from Porto (all of whom were living with children involved in the International Study of Asthma and Allergies in Childhood–phase three), during the year 2002, using a self-administered questionnaire.

Results The prevalence of self-reported drug allergy was 7.8% (181/2309): 4.5% to penicillins or other β-lactams, 1.9% to aspirin or other non-steroidal anti-inflammatory drugs (NSAIDs) and 1.5% to other drugs. In the group 'allergic to β-lactams', the most frequently implicated drug was penicillin G or V (76.2%) followed by the association of amoxicillin and clavulanic acids (14.3%). In the group 'allergic to NSAIDs', acetylsalicylic acid (18.2%) and ibuprofen (18.2%) were the most frequently identified drugs, followed by nimesulide and meloxicam. Identification of the exact name of the involved drug was possible in less than one-third of the patients, more often within the NSAID group (59.5%). Women were significantly more likely to claim a drug allergy than men (10.2% vs. 5.3%). The most common manifestations were cutaneous (63.5%), followed by cardiovascular symptoms (35.9%). Most of the reactions were immediate, occurring on the first day of treatment (78.5%). Only half of the patients were submitted to drug allergy investigations. The majority (86.8%) completely avoided the suspected culprit drug thereafter.

Conclusions The results showed that self-reported allergy to drugs is highly prevalent and poorly explored. Women seem to be more susceptible. β-lactams and NSAIDs are the most frequently concerned drugs.

Keywords drug allergy, drug hypersensitivity, epidemiology, general population

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Introduction

Drug hypersensitivity reactions are the side-effects of drugs taken at a dose that is tolerated by normal subjects and which clinically resemble allergy. When immunologic mechanisms are involved, these reactions are classified as drug allergy [1]. However, many people having experienced a drug hypersensitivity reaction are catalogued as allergic to the drug without any further investigation [2–5]. The diagnostic work-up of a drug hypersensitivity reaction is indeed difficult [5]. The reaction itself is rarely documented, many factors besides the drug can be involved; sometimes the reaction occurred a long time ago and sensitivity could be lost. Another problem is the lack of consensual diagnostic procedures for many drugs, although efforts are being made to overcome this problem [6, 7].

Epidemiological studies about the prevalence of adverse drug reactions, including hypersensitivity, have been focussed mainly on hospitalized patients, hospital admissions and pharmacovigilance post-marketing drug monitoring programmes. It has been estimated that 3–6% of all hospital admissions are because of adverse drug reactions [8–11] and that about 2–20% of hospitalized patients experience some adverse drug reactions [8, 10, 12–15]. In outpatients, the reported incidence of adverse drug reactions can reach 15% [16, 17] and it is also well known that only few reactions are reported to pharmacovigilance agencies [12, 18]. Drug hypersensitivity reactions are thought to represent up to one-third of adverse drug reactions [3]. Surprisingly, studies concerning the prevalence in the general population of adverse drug reactions in general and drug hypersensitivity reactions in particular are scarce compared with studies concerning other allergic diseases, but it may be estimated that 3–7% of the population experience an adverse drug reaction [3, 16, 17, 19]. On the other hand, it is consensual that adverse drug reactions cause significant morbidity and mortality besides huge direct and indirect costs [2, 8, 11, 20]. The role of drug hypersensitivity reactions in that respect is completely unknown.

The aim of this study was to assess the prevalence of self-reported drug allergy in a Portuguese population, with a special focus on β-lactam antibiotics and non-steroidal anti-inflammatory drugs (NSAIDs) [4, 21–25].

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Material and methods

Design of the study

This is a cross-sectional survey of a general adult population from Porto during the year 2002. Two thousand five hundred subjects were invited to complete a self-administered questionnaire to assess the life occurrence of drug hypersensitivity events in adults. The sample consisted of adults (mostly parents) living with children who were participating in the International Study of Asthma and Allergies in Childhood (ISAAC) phase three study in Porto. Children aged 6–7 years were chosen randomly from Porto public schools according to the ISAAC protocol [26]. The term 'allergy' was used in the questionnaire, as it is the most recognized term among the general population (even though drug hypersensitivity would probably be more accurate). Detailed information about the reaction (or the most serious episode if several) was used to better characterize the reactions in terms of clinical symptoms and severity. Information about a previous diagnostic work-up was also analysed.

Statistical analysis

All analyses were performed with the SPSS statistical package (version 11.0) and a two-sided significance level of 5% was used throughout. For the characterization of the study population, a descriptive analysis was done. The prevalence of responses was compared with the Pearson χ^2 test (with the Yates correction when applied) or the Fisher exact test when needed. The odds ratio (OR) and its 95% confidence interval (CI) were also calculated. The Wilcoxon–Mann–Whitney test and Kruskal–Wallis one-way ANOVA were used to compare the age between two or more groups, respectively.

Results

General sample

We evaluated 2309 individuals ranging from 21 to 83 years (mean 36.9 ± 6.1 years) with an approximately equal distribution between sexes (48.4% males). The rate of participation was 92.4% (2309/2500). The prevalence of self-reported drug allergy was 7.8% (181/2309): 4.5% considered themselves allergic to penicillins or other β-lactams, 1.9% to aspirin or other NSAIDs and 1.5% stated to be allergic to other drugs. Women were significantly more likely to have self-reported drug allergy (OR = 2.05, $P < 0.001$, 95% CI = 1.04–2.82) and to be allergic to β-lactams (OR = 2.08, $P = 0.001$, CI 1.36–3.17), but not significantly higher to NSAIDs (Table 1). There were no significant age differences between the individuals with or without self-reported drug allergy and also between the individuals with self-reported drug allergy to β-lactams or NSAIDs.

Subjects with self-reported drug allergy

The 181 subjects with self-reported drug allergy were aged from 24 to 64 years (mean 36.9 ± 6.4 years) and 67.9% were women. Among this population, 96 (53.0%) considered themselves to be allergic to β-lactams, 37 (20.4%) to NSAIDs and eight (4.4%) to both. Regarding other drugs responsible, pomades were involved in eight (4.4%) subjects, sulphametoxazol/trimetroprim and other antibiotics in four (2.2%) and five (2.8%) individuals, respectively. The identification of the drug was not given by eight subjects (4.4%). There were no significant gender differences between the individuals with self-reported drug allergy to β-lactams or NSAIDs. From the 171 subjects that answered the question about the way the diagnosis was made, 50 (29.3%) stated that they have been told by the doctor they were allergic. About half of the subjects (67 out of the 123 who answered the question) had not been submitted to any diagnostic procedure, 26% underwent blood analysis and 22.7% skin testing.

Table 1. Differences in self-reported drug allergy in women and men

	No. (%) with hypersensitivity	OR (95% CI)	*P*–value
Any drugs			
Women	122/1192 (10.2)	2.05 (1.04. 2.82)	< 0.001
Men	59/1117 (5.3)		
NSAIDs			
Women	29/1192 (2.4)	1.61 (0.88. 2.95)	>0.05
Men	17/1117 (15)		
β-Lactams			
Women	71/1192 (6.0)	2.08 (1.36. 3.17)	0.001
Men	33/1117 (3.0)		

OR, odds ratio; CI, confidence interval; NSAIDs, non-steroidal anti-inflammatory drugs.

In the group 'allergic only to β-lactams', 21/96 (21.9%) recalled the exact drug that caused the reaction and the most frequently implicated was penicillin G or V (76.2%), followed by the association amoxicillin/clavulanic acid (14.3%). In the group 'allergic to NSAIDs', 22/57 (59.5%) could remember the exact drug involved in the reaction. Acetylsalicylic acid and ibuprofen were identified by eight subjects (18.2%). Nimesulide was mentioned by three participants and meloxicam by two. People considering themselves allergic to NSAIDs identified more often the name of the involved drug than the ones with reactions to β-lactams (OR = 5.24, $P < 0.001$, 95% CI = 2.32–11.84).

Recalled clinical manifestations (Table 2) were separated into cutaneous, nasal/ocular, bronchial, cardiovascular and digestive reactions. The most common manifestations were cutaneous (63.5%), followed by cardiovascular (35.9%), bronchial (14.4%), nasal/ocular (12.7%) and gastrointestinal symptoms (11.6%). Comparisons between individuals with self-reported β-lactam and NSAID allergy showed only significant differences for the frequency of gastrointestinal symptoms: 6.3% in the β-lactam group vs. 24.3% in the NSAID group ($P = 0.006$). Women reported symptoms more often than men, but this difference was only significant for gastrointestinal symptoms (OR = 5.26, $P = 0.031$, 95% CI = 1.18–23.39) and marginally significant for cardiovascular symptoms (OR = 2.04, $P = 0.06$, 95% CI = 1.02–4.05) (Table 3).

Only 125/181 (69.1%) subjects with self-reported drug allergy answered the question about the route of administration of the drug, which was oral for 56%, parental for 40% and both oral and parental for five (4%) individuals.

Table 2. Relative frequency of clinical manifestations, as reported by the subjects ($n = 181$)

Question	%	Question	%
Itching on the skin	30.4	Sweating, fainting	21.5
Skin rash or urticaria	47.5	Hypotension	13.3
Swelling or angiooedema	20.4	Loss of consciousness	8.8
Redness, itching or secretion of the eyes	6.6	Tachycardia /palpitations	11.6
Sneezing, itching, blockage or secretion of the nose	10.5	Difficulty to swallow or to speak	6.1
Shortness of breath or cough	13.3	Nausea or stomach-ache	7.7
Wheezing	6.6	Vomiting or diarrhoea	7.2
Pallor	12.7	Other symptoms	9.4

Table 3. Differences in clinical manifestations during the episode of self-reported drug allergy between β-lactam and NSAID groups and between women and men

Manifestations	No. (%) with manifestation	OR (95% CI)	*P*-value
Cutaneous			
β-Lactams	61/96 (63.5)	2.05 (0.95. 4.42)	0.09
NSAIDs	17/37 (45.9)		
Women	79/122 (64.8)	1.17 (0.62. 2.23)	>0.05
Men	36/59 (61.0)		
Nasal/ocular			
β-Lactams	11/96 (11.5)	0.67 (0.23. 1.96)	>0.05
NSAIDs	6/37 (16.2)		
Women	18/122 (14.8)	1.87 (0.66. 5.31)	>0.05
Men	5/59 (8.5)		
Bronchial			
β-Lactams	13/96 (13.5)	1.29 (0.39. 4.25)	>0.05
NSAIDs	4/37 (10.8)		
Women	19/122 (14.8)	1.37 (0.54. 3.47)	>0.05
Men	7/59 (11.9)		
Cardiovascular			
β-Lactams	29/96 (30.2)	0.71 (0.32. 1.57)	>0.05
NSAIDs	14/37 (37.8)		
Women	50/122 (41.0)	2.04 (1.02. 4.05)	0.06
Men	15/59 (25.4)		
Gastrointestinal			
β-Lactams	6/96 (6.3)	0.21 (0.07. 0.63)	0.006
NSAIDs	9/37 (24.3)		
Women	19/122 (15.6)	5.26 (1.18. 23.39)	0.031
Men	2/59 (3.4)		

NSAIDs, non-steroidal anti-inflammatory drugs.

Out of 153, 114 (74.5%) did not recall a previous contact with the same drug. For the 139 individuals who answered this question, the reaction occurred during the first day of treatment for 69.1%. According to the 144 valid answers, the time delay between the last intake of the drug and the reaction was less than 1 h in 43.1% of the cases, more than 1 h but less than 1 day in 35.4% and more than 24 h in 21.5%. Women and men did not report different times. There was a significant association between the route of administration and the time to reaction ($P = 0.017$) with the parental route being responsible for more reactions occurring within the first hour (58.7% vs. 35.3%) (Table 4). There was no significant association between the time interval of the intake and the reaction among reactants to β-lactams vs. NSAIDs, although 38.7% of the latter group reacted within 1 h vs. 53.5% in the former group. In fact, in 57.8% of the β-lactam group the parental route was used as compared with only 20.8% in the NSAID group ($P = 0.004$).

Table 4. Chronology of the reactions according to the route of administration and the type of drugs (β-lactams or NSAIDs)

	No. (%) with manifestation				
	< 1 h	1 h to 1 day	>1 day	Total	*P*-value
Administration					
Oral medication	24 (35.3)	26 (38.2)	18 (26.5)	68 (100.0)	0.017
Parental route	27 (58.7)	15 (32.6)	4 (8.7)	46 (100.0)	
Drugs					
β-Lactams	38 (53.5)	25 (35.2)	8 (11.3)	71 (100.0)	>0.05
NSAIDs	12 (38.7)	13 (41.9)	6 (19.4)	31 (100.0)	

NSAIDs, non-steroidal anti-inflammatory drugs.

In 57.5% (85 out of 148 who answered this question) of the individuals, it took more than 1 day to recover completely from the reaction. Only 62.6% (92 out of 147) looked for medical assistance because of the reaction. Although not significant, there was a tendency within the group with isolated cutaneous manifestations to look for medical help more often than those with other manifestations (OR = 2.39, $P = 0.08$, 95% CI = 0.99–5.78).

The majority of subjects (86.8%, 138 out of 159 who answered this question) completely avoided the suspected culprit drug thereafter, and 20 out of the 21 (13.2%) who took it again relapsed. Only 13.3% (24 of 181) of the participants stated that they would like to further investigate the reaction.

Discussion

The prevalence of self-reported drug allergy in a general population has never been reported in the literature. Surprisingly, it was not lower (7.8%) than the prevalence for inpatients. Similarly, except for NSAIDs, women were more frequently concerned than men [27–30]. The high rate of participation (92.4%) strengthens the data. If we consider that non-returned or unanswered questionnaires would be from people without self-reported drug allergy the prevalence is still high (181/2500, 7.2%).

In agreement with other studies [8, 21–23, 30], the drugs suspected to be responsible for most self-reported drug allergies were β-lactams and NSAIDs. It must be said that the consumption of antibiotics and NSAIDs in Portugal is one of the highest in Europe and that most of the drugs are easily obtained over the counter [24, 25]. Most of the people with a reported drug allergy to any β-lactam will consider themselves allergic to all penicillins and do not recall the exact drug name, although specific reactions to different molecules are possible [31–34]. This reflects in fact the common medical practice in Portugal and in other countries of banning all β-lactams in patients who experienced a reaction to one

antibiotic of this group without any diagnostic work-up [3–5, 21, 35–37]. On the other hand, people with a reported drug allergy to a NSAID will recall more exactly the drug involved and do not assume so easily that they should avoid the whole group. This again reflects common medical practice in Portugal and other countries where NSAIDs are usually considered safe in patients having experienced a cutaneous hypersensitivity reaction to aspirin; nimesulide [38, 39] or meloxicam [40, 41] are frequently proposed instead.

Regarding manifestations, skin reactions of immediate delay were the vast majority as stated by others [4, 14, 23, 42]. The fact that most reactions occurred during the first day of treatment and within 1 h of drug administration suggests that IgE-dependent reactions are more frequent than T cell-dependent reactions. The fact that the majority of the individuals do not recall a previous contact with the drug suspected to be causing the reaction could be explained by several factors: a long time interval since the sensitizing treatment, unperceived intakes of the same or similar drugs or by the occurrence of non-allergic reactions.

Many people did not seek medical help because of the reaction. Only 62.6% did so, and were the ones with pure dermatological manifestations that more often looked for assistance. After a possible allergic reaction, most people avoided further contact with the suspected causative drug and only 13.2% took it again. Among those, the majority had another reaction, demonstrating true drug hypersensitivity. A firm diagnosis was approached with the help of blood analyses and/or skin testing in less than half of the cases and about half were apparently not submitted to any diagnostic investigation. This might be due either to a low number of centres exploring drug allergy or to the fact that most of the people were convinced about their diagnosis (since only 13.3% of the participants referred that they would like to be contacted to further investigate the reaction).

This study shows that self-reported drug allergy is highly prevalent in the adult Portuguese population, women being more susceptible. Dermatological reactions are the most frequent. Drug hypersensitivity reactions are, however, poorly investigated in many cases, leading to an uncertain diagnosis of allergy and possibly to the prescription of potentially less effective and/or more toxic drugs. Direct and indirect costs are not evaluated [35–37, 43].

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References

1 Johansson S, Hourihane J, Bousquet J et al. A revised nomenclature for allergy. An EAACI position statement from the EAACI nomenclature task force. Allergy 2001; 56:813–24.
2 Preston SL, Briceland LL, Lesar TS. Accuracy of penicillin allergy reporting. Am J Hosp Pharm 1994; 51:79–84.
3 Demoly P, Bousquet J. Epidemiology of drug allergy. Curr Opin Allergy Clin Immunol 2001; 1:305–10.
4 deShazo R, Kemp S. Allergic reactions to drugs and biological agents. JAMA 1997; 278:1895–1906.
5 Vervloet D, Durham S. Adverse reactions to drugs. Br Med J 1998; 316:1511–4.
6 Brockow K, Romano A, Blanca M, Ring J, Pichler W, Demoly P. General considerations for skin test procedures in the diagnosis of drug hypersensitivity. Allergy 2002; 57:45–51.
7 Aberer W, Bircher A, Romano A et al. Drug provocation testing in the diagnosis of drug hypersensitivity reactions: general considerations. Allergy 2003; 58:854–63.
8 Lazarou J, Pomeranz BH, Corey PN. Incidence of adverse drug reactions in hospitalized patients. A meta-analysis of prospective studies. JAMA 1998; 279:1200–5.
9 Lakshmanan M, Hershey C, Breslau D. Hospital admissions caused by iatrogenic disease. Arch Intern Med 1986; 146:1391–4.
10 Pouyanne P, Haramburu F, Imbs JL, Begaud B. Admissions to hospital caused by adverse drug reactions: cross sectional incidence study. Br Med J 2000; 320:1036.
11 Sheikh A, Alves B. Hospital admissions for acute anaphylaxis: time trend study. Br Med J 2000; 320:1441.
12 Classen DC, Pestotnik SL, Evans RS, Burke JP. Computarized surveillance of adverse drug events in Hospital patients. JAMA 1991; 266:2847–51.
13 Miller R. Drug surveillance utilizing epidemiological methods: a report from the Boston collaborative drug surveillance program. Am J Hosp Pharm 1973; 30:584–92.
14 Bowrey DJ, Morris-Stff GJ. Drug allergy: fact or fiction? Int J Clin Pract 1998; 52:20–1.
15 Bates DW, Cullen DJ, Laird N et al. Incidence of adverse drug events and potential adverse drug events. JAMA 1995; 274:29–34.
16 Ibia EO, Schwartz R, Wiedermann BL. Antibiotic rashes in children: a survey in a private practice setting. Arch Dermatol 2000; 136:849–54.
17 Impicciatore P, Choonara I, Clarkson A, Provasi D, Pandolfini C, Bonati M. Incidence of adverse drug reactions in paediatric in/outpatients: a systematic review and meta-analysis of prospective studies. Br J Clin Pharmacol 2001; 52:77–83.
18 Smith CC, Bennett PM, Pearce HM et al. Adverse drug reactions in a hospital general medical unit meriting notification to the committee on safety of medicines. Br J Clin Pharmacol 1996; 42:423–9.
19 Hedman J, Kaprio J, Poussa T, Nieminen M. Prevalence of asthma, aspirin intolerance, nasal polyposis and chronic obstructive pulmonary disease in a population- based study. Int J Epidemiol 1999; 28:717–22.
20 Classen D, Pestotnik SL, Evans R, Lloyd J, Burke J. Adverse drug events in Hospitalized patients: excess length of stay, extra costs and attributable mortality. JAMA 1997; 277:301–6.
21 Weiss M, Adkinson NF. Immediate hypersensitivity reactions to penicillin and related antibiotics. Clin Allergy 1988; 18:515–40.
22 de Weck AL. Drug allergy, immunotherapy, immune complexes and anaphylaxis. Curr Opin Immunol 1990; 2:548–57.
23 Bigby M. Rates of cutaneous reactions to drugs. Arch Dermatol 2001; 137:765–70.
24 Molstad S, Lundborg CS, Karlsson AK, Cars O. Antibiotic prescription rates vary markedly between 13 european countries. Scand J Infect Dis 2002; 34:366–71.
25 Cars O, Molstad S, Melander A. Large variation in antibiotic utilization between the countries in the European union. Lancet 2001; 357:1851–2.
26 Asher MI, Keil U, Anderson HR et al. International Study of Asthma and Allergies in Childhood (ISAAC): rationale and methods. Eur Respir J 1995; 8:483–91.
27 Barranco P, Lopez-Serrano MC. General and epidemiological aspects of allergic drug reactions. Clin Exp Allergy 1998; 28:S61–2.
28 Haddi E, Charpin D, Tafforeau M et al. Atopy and systemic reactions to drugs. Allergy 1990; 45:236–9.

29 Asero R. Detection of patients with multiple drug allergy syndrome by elective tolerance tests. Ann Allergy Asthma Immunol 1998; 80:185–8.
30 Naldi L, Conforti A, Venegani M et al. Cutaneous reactions to drugs. An analysis of spontaneous reports in four Italian regions. Br J Clin Pharmacol 1999; 48:839–46.
31 Baldo BA. Penicillins and cephalosporins as allergens – structural aspects of recognition and cross-reactions. Clin Exp Allergy 1999; 29:744–9.
32 Romano A, Mondino C, Viola M, Montuschi P. Immediate allergic reactions to beta-lactams: diagnosis and therapy. Int J Immunopathol Pharmacol 2003; 16:19–23.
33 Torres MJ, Romano A, Mayorga C et al. Diagnostic evaluation of a large group of patients with immediate allergy to penicillins: the role of skin testing. Allergy 2001; 56:850–6.
34 Romano A, Mayorga C, Torres MJ et al. Immediate allergic reactions to cephalosporins: cross-reactivity and selective responses. J Allergy Clin Immunol 2000; 106:1177–83.
35 Pilzer JD, Burke TG, Mutnick AH. Drug allergy assessment at a university hospital and clinic. Am J Health-Syst Pharm 1996; 53:2970–5.
36 Tripp DM, Brown GR. Pharmacist assessment of drug allergies. Am J Health-Syst Pharm 1993; 50:95–8.
37 Preston SL, Briceland LL, Lesar TS. Accuracy of penicillin allergy reporting. Am J Health-Syst Pharm 1994; 51:79–84.
38 Quaratino D, Romano A, Papa G et al. Long-term tolerability of nimesulide and acetaminophen in nonsteroidal antiinflammatory drug-intolerant patients. Ann Allergy Asthma Immunol 1997; 79:47–50.
39 Valero A, Marti E, Gonzalez MA, GETNIA (Study group of tolerance to numesulide in NSAIDs intolerance patients). Tolerance to nimesulide in patients with intolerance to NSAIDs (abstract). International Symposium on Aspirin Intolerance and Related Syndromes: a Multidisciplinary Approach. Rome, November 1999.
40 Quaratino D, Romano A, Di Fonso M et al. Tolerability of meloxicam in patients with histories of adverse reactions to nonsteroidal anti-inflammatory drugs. Ann Allergy Asthma Immunol 2000; 84:613–7.
41 Nettis E, Di Paolo R, Ferrannini A, Tursi A. Meloxicam in hypersensitivity to NSAIDs. Allergy 2001; 56:803–4.
42 Kerr JR. Penicillin allergy: a study of incidence as reported by patients. Br J Clin Pract 1994; 48:5–7.
43 Adkinson N. Drug allegy. In: Middlenton E. Jr, Reed C, Ellis E, Adkinson F. Jr, Yunginger J, Busse W, eds. Allergy Principles and Practice. St Louis, MO: Mosby. Year Book, Inc, 1998; 1212–24.