CLINICAL SCIENCE

Drug hypersensitivity in students from São Paulo, Brazil

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BACKGROUND: Drug hypersensitivity is responsible for substantial mortality and morbidity, and increased health costs. However, epidemiological data on drug hypersensitivity in general or specific populations are scarce.

METHODS: We performed a cross-sectional survey of 1015 university students, using a self-reported questionnaire.

RESULTS: The prevalence of self-reported drug hypersensitivity was 12,11% (123/1015). The most frequently implicated drugs were non-steroidal anti-inflammatory drugs (45,9%) and beta-lactam and sulfonamide antibiotics (25,40%). The majority of the patients reported dermatological manifestations (99), followed by respiratory (40), digestive (23) and other (19). Forty-five patients had an immediate type reaction, and 76,72% (89) had the drug by oral route.

CONCLUSION: The results showed that drug hypersensitivity is highly prevalent in university students, and that non-steroidal anti-inflammatory drug and antibiotics (beta-lactams and sulfonamide) are the most frequently concerned drugs.

KEYWORDS: Drug eruption; Drug hypersensitivity; Epidemiology; questionnaire; Students.

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INTRODUCTION

Drug hypersensitivity reactions are initiated by an exposure to a drug at a dose tolerated by a normal person, and they clinically resemble allergy. Drug allergy is a term that should be used when the drug hypersensitivity reaction is initiated by a specific immunological mechanism.[1]

There are few studies on the prevalence of drug hypersensitivity reactions in the general population, but it may be estimated that about three to four percent of children and more than seven percent of the adult population experience a drug hypersensitivity reaction.[2-4]

The aim of this study was to estimate the prevalence of self-reported drug hypersensitivity and its characteristics in a university population from São Paulo, Brazil.

MATERIALS AND METHODS

We performed a cross-sectional survey of 1015 students from a university in São Paulo, Brazil. During October and November of 2007, participants were approached in the classroom on different days and times and were invited to answer a self-administered questionnaire.[5] The sample consisted of 43% of all registered students, which included students in Medicine, Veterinary Medicine, Biomedicine, Pharmacy, Odontology, Physical Education, Physiotherapy and Nursing.

Prior to the study, all subjects received information about the study, and a written informed consent was obtained from each individual. The protocol was approved by the respective institutional review boards.

Detailed information about the type of reaction and the time of its appearance, the drug involved with the allergic manifestation, the route of administration and the need of medical treatment were obtained to characterize the studied population. We also included the frequency of atopic diseases among the group (asthma, rhinitis and atopic dermatitis).

The term ''allergy'' was used in the questionnaire, as it is the most recognized term among the general population, even though ''drug hypersensitivity'' is probably be more accurate.

Data collected were transcribed to a database (Epi-info 6.04), and the frequency of affirmative answers to each question was analyzed. For analysis of the results, we applied the following tests: x^2 test (Siegel) to study the possible associations between the studied variables and Cochran G test (Siegel) to study the concomitance among

Table 1 - Type of drug and clinical manifestations.

Drug	Cutaneous	Respiratory	Digestive
NSAID	42	23	12
β-lactams and sulfonamide antibiotics	32	11	6
Others	24	5	4
Total	98	39	22

NSAID, non-steroidal anti-inflammatory drugs

the presented symptoms. The level of rejection of the null hypothesis was fixed at 0.05 or 5%.

RESULTS

We evaluated 1015 students ranging from 17 to 56 years of age (mean 23.05 $\pm$ 5.97 years), most of whom were female (74.8%). The prevalence of self-reported drug allergy was 12.11% (123/1015). The doctor diagnosed drug allergy in 77 (62.60%) out of the participants. However, only 47 (38.52%) required any kind of treatment. The majority of the students (64.22%) reported to have an atopic disease.

The 123 subjects with self-reported drug allergy were between 18 to 56 years of age (mean 23.14), and 79.7% were women. Among this population, 56 (45.90%) considered themselves allergic to NSAIDs, 35 (28.68%) to β–lactams and sulfonamide antibiotics and 31 (25.40%) to other drugs, such as other antibiotics and corticosteroids. We excluded one participant from the previous analysis due the recall of being allergic to both β–lactams and NSAIDs. We did not observe a significant gender difference between the types of drugs.

Recalled clinical manifestations were separated into cutaneous, digestive, respiratory and other reactions. Dermatological manifestations were frequently described (99 subjects) in cases of allergy to NSAID, β-lactams, sulfonamide antibiotics and other drugs, followed by respiratory (40 subjects), digestive (23 subjects) and other symptoms (19 subjects). However, we did not observe any significant statistical difference between the class of drugs and the types of reaction (Table 1).

Out of 122 subjects, the age at which reactions occurred was most common in 10 to 20 incomplete years (45.90%) followed by 0 to 10 years (35.24%) and 20 years or more (18.85%), which was lower than the previous two records ($p < 0.001$). We noticed that among 0 to 10 years, β–lactams, sulfonamide antibiotics and NSAIDs were more responsible for drug hypersensitivity than other drugs ($p < 0.02$) (Table 2).

According to the time of reaction after administration, 45 out of 118 (38.13%) reported to react in less than an hour, 50 (42.37%) reacted in more than an hour or in less than a day

Table 2 - Type of drug and age of reaction.

	Age of reaction (years)		
Type of drug	0 to 9	10 to 19	> 20
NSAID	18	23	6
β-lactams and sulfonamide antibiotics	20	13	2
Other	5	20	6
Total	43	56	14

NSAID, non-steroidal anti-inflammatory drugs

Table 3 - Chronology of the reactions according to the route of administration.

	Interval time of manifestation			
Route of administration	< 1 h	1 h to 1 day	> 1 day	Total
Oral	27	42	16	85
Parenteral	13	6	1	20
Other	0	1	5	6
Total	40	49	22	

and 23 (19.49%) reacted in more than a day. We observed that late reactions (occurring after a day) were less prevalent in comparison to the other two ($p < 0.01$) (Table 3).

Out of the 116 subjects that answered the question on the route of drug administration, 89 (76.72%) reported oral, 20 (17.24%) parenteral and 7 (6.03%) other routes, which included topical ($p < 0.001$). We did not include seven subjects, who notified both ''oral'' and ''parenteral'' as routes of administration (Table 3).

At the time of reaction, 107 out of 116 participants (92.24%) reported that the duration of drug usage was less than a week. In five subjects (4.31%), the reaction started for more than a week but less than a month after the drug started. The reaction initiated after one month of use in 4 (3.44%) individuals ($p < 0.001$).

DISCUSSION

Self-reported drug hypersensitivity is a common problem in daily clinical practice and has a considerable impact on prescription choices[5]. Although there are few reports on the epidemiology of drug hypersensitivity, there are some data suggesting that the prevalence of these reactions are similar in a university students group and the general population.[5,6] That's the reason why in our survey we decided to focus on this specific group. We found a high prevalence of drug allergy (12.11%) among university students in São Paulo. Despite high level of prevalence, medical diagnosis of drug allergy was reported in less than 65% of individuals. This observation suggests that the remaining students may be self-diagnosed. Assuming that all doctors made accurate diagnoses and that the reactions not seen by doctors were not hypersensitivity reactions, the prevalence of drug hypersensitivity in our study was 7.8%, which is very close to that reported by Falcão et al. in university students from Porto, Portugal.[6] Moreover, less than half of them required treatment, which is uncommon among hypersensitivity reactions, indicating that some people may be misdiagnosed.

In agreement with other studies,[5,7-11] drugs that were suspected to be responsible for most of the self-reported drug hypersensitivity were NSAIDs and β-lactams, but sulfonamide antibiotics were also responsible. Antibiotics are largely used during childhood and teenage years for treating common infections, specially these two classes.[12] More than two thirds of the reactions were reported to happen during the first 20 years of life, and in most cases, the drug was taken orally. Most of the drugs are easily obtained over the counter in Brazil. Moreover, the prevalence of self-medication in children and young adults is high in our country,[13] and NSAIDs are the most consumed pharmacological group.[14]

Regarding manifestations, skin reactions were the vast majority as stated by others.[15-18] The fact that most reactions occurred during the first day of treatment suggests that IgE-dependent reactions are more frequent than T cell-dependent reactions. However, we should take into consideration that most of the NSAID reactions are not IgE-dependent, but rather directly related to the inhibition of the enzyme cyclooxygenase 1 (COX-1) and clinically similar to an immediate type I reaction with urticaria, angioedema and anaphylaxis.[19]

This study shows the high prevalence of hypersensitivity reactions in university students in São Paulo, Brazil. However, there are limitations to this study. Self-reported data are subject to recall bias as well as potential problems with the validity of the responses. Highly educated individuals may improve the quality and accuracy of self-reported information. On the other hand, most of these students are from medical or allied health schools, and part of them may be self-diagnosed. Because only non-identified data were collected, we did not have the means to further verify individual reactions. Despite such limitations, it is a unique form of investigation among the drug hypersensitivity literature.[2-4,6] Although many of these recalls might not reflect true hypersensitivity, these individuals will probably be labeled as allergic to drugs and be given second-line treatments, which are usually more expensive and less effective.

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