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Immediate Type Drug Hypersensitivity Reactions and Associated Risk Factors in an Adult Turkish Men Population

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ABSTRACT

The study aimed to assess the prevalence and associated risk factors of immediate-type hypersensitivity reactions (HRs) to drugs in workers.

The data consisted of 1152 questionnaires obtained from adult men that consisted of questions on HRs induced by drugs. The prevalence of self-reported drug HRs was 3.6% for all reactions. HRs were most common to beta-lactam antibiotics (51.2%) followed by nonsteroid antiinflammatory drugs (NSAIDs) (41.5%). Multivariate analysis showed that family atopy was associated with drug HRs to both antibiotics (Odds Ratio (OR) 95% Confidence Interval (CI) (3.32 (1.15–9.56)) and NSAIDs (3.70 (1.09–12.51)). Drug HRs of any type were associated with atopic family history (3.23 (1.43–7.24)), ever asthma diagnosis (2.74 (1.07–7.02)), ever allergic rhinitis (2.70 (1.25–5.84)), and ever eczema (3.80 (1.55–9.30)). Drug related skin manifestations were associated with family history of atopic diseases (4.07 (1.76–9.41)), ever allergic rhinitis (2.84 (1.24–6.5)), ever asthma diagnosis (3.16 (1.19–8.39)), and ever eczema diagnosis (4.59 (1.82–11.57)). Systemic manifestations of drug HRs were associated with only asthma diagnosis (4.66 (1.25–17.41)).

Risk groups should be followed closely as candidates for immediate type HRs to antibiotics and NSAIDs in also relatively healthy and young aged adult men.

Key words: Drug Allergy; Epidemiology; Hypersensitivity; Risk Factors

INTRODUCTION

Hypersensitivity reactions to drugs are common problems in general adult population. In spite of developments in the area of allergy in recent decades,

data on the prevalence and related factors of hypersensitivity reactions to drugs in outpatient population is sparse. Most of the reports on drug reactions focused on in-patient cases. Prevalence of adverse drug events has been reported as 10.4% in general practice patients.¹ About one-fifth of adverse drug reactions are classified as hypersensitivity reactions.² In a previous study, drug allergy prevalence was found to be 7.8% in a general adult population.³

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Prevalence of drug reactions varies according to status of the patients such as gender, age, and morbidity. Female gender and older age were reported as risk factors for drug reactions.^{1,3} The peak prevalence of adverse drug reactions were reported at age 65 and above.¹ Drug allergy prevalence seems to be two-fold higher in female population³. Among other conditions atopy was reported as a risk factor for both nonsteroid antiinflammatory drugs (NSAIDs) and antibiotic drug allergy.^{4,5} Among antibiotics penicillins and sulfa drugs were reported to have higher incidence of reactions^{6,7}. Because hypersensitivity is a consequence of frequent exposure, it may be assumed that chronic diseases causing exposure to drugs may have increased risk for drug hypersensitivity reactions.

Different prevalence rates of drug hypersensitivity reactions and their clinical associations may be originated from older ages or morbidities of the patients studied. To minimize these effects originating from gender, ages, and morbidities, we planned to investigate drug hypersensitivity reactions in young and moderate aged adult men workers who may represent relatively healthy population. There is no data on drug hypersensitivity reactions in worker population also. The present study aimed to assess the prevalence and related risk factors of immediate type hypersensitivity reactions to drugs in young and moderate aged adult workers.

SUBJECTS AND METHODS

This cross-sectional study consists of results of 1152 adult men aged between 21 years and 52 years, working in different sections of a factory. The factory is a big complex serving production, repair and restoration of railway systems. Factory is located in Eskişehir which is a town in western part of inner Anatolia with a population of about six-hundred thousand. Study was conducted between November 2007 and March 2008. Information was collected by an interviewer who was educated on the structured questionnaire before use; the questionnaire was prepared prior to the study. The test-retest repeatability of questionnaire was found to be excellent in a group of 30 subjects, who filled the questionnaire two to three weeks apart.

The questionnaire consisted of questions on immediate type hypersensitivity reactions induced by drugs (itching on the skin, skin rash or hives (urticaria),

swelling of the lips, tongue, eyes or face=angioedema, shortness of breath, hypotension, loss of conscience or coma following drug intake without any other reason), the name of the drug causing the allergic reaction, and time of the reaction.

The questionnaire added additional knowledge on the physician's diagnosis of allergic diseases, asthma, allergic rhinitis, and eczema. Asthma, allergic rhinitis, and eczema information was self-reported based on of having ever been diagnosed by a doctor. Family history of any allergic disease including drug allergy, asthma, allergic rhinitis, and eczema was accepted as atopic family history. The questionnaires also included demographical data as well as additional data on the diagnosis of other chronic systemic diseases (heart disease, diabetes mellitus, goitre, systemic hypertension, and others if any).

The study was approved by the local ethics committee and the subjects gave informed consent for the study.

Statistical Analysis

Values are expressed as mean $\pm$ SD (standard deviation). Chi-square test was used to compare variables between groups. Logistic regression analysis was used to assess the independent association between possible risk factors and drug hypersensitivity reactions for all and each hypersensitivity reaction separately. The strength of the relationship between risk factors and the reactions was evaluated by calculating adjusted odds ratios (OR) and their 95% Confidence Interval (CI) for all the factors tested. Variables included in the multivariate logistic regression model were selected from these results, which had a significance of less than 0.05 in univariate analysis. Age was analyzed as a continuous covariate. All other variables were coded as categorical covariates that were incorporated to the model dichotomously. Differences were considered as statistically significant if $p < 0.05$. The data was analyzed with SPSS computer program for Windows version 13.0.

RESULTS

The mean age of the patients was 42.9 ± 6.5 years. Education level of the subjects were as follows: Five-grade elementary school; 144(12.5%) subjects, eight-grade elementary school; 84(7.3%) subjects, eight-grade technical elementary school; 225(19.5%)

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subjects, high-school; 32(2.8%) subjects, technical high-school; 645(56%) subjects and university; 21 (1.8%) subjects. The prevalence of self-reported immediate type drug hypersensitivity reactions was 3.6% (n= 41) for all type of reactions. Of all patients who reported drug hypersensitivity, 46.3% reported itching on the skin (1.6% of all subjects), 53.6% for hives and urticarial complaints (1.9% of all), 12.2% for angioedema (0.4% of all), 19.5% for shortness of breath (0.7% of all), 7.3% for hypotension and loss of conscience (0.3% of all). Immediate type hypersensitivity reactions were the most common to antibiotics (n=21, 51.2%), followed by NSAIDs (n=17, 41.5%). Two patients reported drug reaction after intramuscular injection whereas the other reactions occurred via oral intake. Only three subjects reported hypersensitivity reactions to other drugs (one to a retinoid (acitretin), one to proton-pump inhibitor (lansoprazol), and one to montelukast. Seventy-eight percent of the subjects who reported drug hypersensitivity reaction recall a previous contact with the responsible drugs. Only three of the subjects who reported hypersensitivity reaction (7.3%) did not report a previous contact. The other 6 subjects (14.6%) did not recall a previous contact with the responsible drug. All reactions were occurred in the first day of the drug use mostly within the first hour of drug intake (38 subjects). The other 3 subjects reported reaction time

after one hour of drug intake within the same day. But they did not recall the exact reaction time.

Table 1 shows drug reactions to all drugs, antibiotics, and NSAIDs and their associations with the comorbidities of the subjects in univariate analysis. Family atopy, doctor diagnosis of asthma, allergic rhinitis, and eczema were associated with drug hypersensitivity reactions in univariate analysis.

The prevalences of ever doctor-diagnosed asthma, ever allergic rhinitis, ever eczema, and diagnosis of any chronic-systemic disease were as follows ; 4.9%(57 subjects), 10.4%(120 subjects), 4.8% (55 subjects), and 17.4%(200 subjects). Of chronic systemic diseases, current prevalence of systemic hypertension was 9.4% (108 subjects), current prevalence of any heart disease was 4.6% (53 subjects), current prevalence of diabetes was 3.2%(37 subjects), and current prevalence of goitre was 2.3% (27 subjects).

We classified drug-induced immediate type hypersensitivity reactions to two groups; skin manifestations (itch, rashes, and urticarial type reactions) and systemic type reactions (shortness of breath, angioedema, hypotension, loss of conscience or coma). Skin manifestations consisted most of the reactions 82.9%(34 subjects) and systemic type reactions were 36.3% (15 subjects).

Table 1. Reactions to all drugs, antibiotics, and NSAIDs and their association with the characteristics of patients in univariate analysis.

Topics	Family atopy (n=84)	Ever asthma (n=57)	Ever A. rhinitis (n= 120)	Ever eczema (n= 55)	Any systemic disease (n=200)
Drug reaction to any group					
No (%) with HRs	11 (26.8)	8 (19.5)	13 (31.7)	8 (19.5)	9 (21.9)
OR	5.12***	5.21**	4.36***	5.55***	1.35
(95% CI)	(2.47-10.65)	(2.28-11.90)	(2.19-8.66)	(2.42-12.71)	(0.64-2.88)
Drug reaction to antibiotics					
No (%) with HRs	6 (28.6)	4 (19.0)	7 (33.3)	3 (14.3)	4 (19.0)
OR	5.40**	4.74*	4.50**	3.39	1.12
(95% CI)	(2.04-14.31)	(1.54-14.58)	(1.78-11.39)	(0.97-11.88)	(0.37-3.37)
Drug reaction to NSAIDs					
No (%) with HRs	4 (23.5)	2 (11.7)	4 (23.5)	4 (23.5)	5 (29.4)
OR	4.06*	2.59	2.70	6.95**	2.01
(95% CI)	(1.29-12.73)	(0.58-11.63)	(0.87-8.43)	(2.17-22.32)	(0.70-5.77)

A= Allergic, HRs: Hypersensitivity Reactions, NSAIDs= Non Steroidal Anti-inflammatory Drugs.

OR= Odds Ratio, CI= Confidence Interval, *: $p<0.05$, **: $p<0.01$, ***: $p<0.001$

Table 2. Associations between skin and systemic type hypersensitivity reactions and related factors in univariate analysis

Topics	Family atopy (n=84)	Ever asthma (n=57)	Ever A. rhinitis (n= 120)	Ever eczema (n= 55)	Any systemic disease (n=200)
Skin manifestations					
No (%) with HRs	11 (26.8)	8 (19.5)	12(29.3)	8 (19.5)	7 (17)
OR	6.85***	6.65***	5.10***	7.16***	1.24
(95% CI)	(3.21-14.59)	(2.86-15.44)	(2.46-10.59)	(3.06-16.7)	(0.53-2.89)
Systemic manifestations					
No (%) with HRs	4 (.9.76)	4 (9.76)	5 (12.2)	2 (4.86)	4 (9.76)
OR	4.81*	7.37**	4.44*	3.08	1.75
(95% CI)	(1.50-15.43)	(2.27-23.91)	(1.49-13.23)	(0.68-14.02)	(0.55-5.54)

A= Allergic, HRs: Hypersensitivity Reactions, NSAIDs= Non Steroidal Anti-inflammatory Drugs.

OR= Odds Ratio, CI= Confidence Interval, *: $p<0.05$, **: $p<0.01$, ***: $p<0.001$

Table 2 shows associations between skin and systemic type hypersensitivity reactions and related factors in univariate analysis. Skin manifestations of drug hypersensitivity reactions were related with atopic family history, ever asthma diagnosis, ever allergic rhinitis, and ever eczema. Systemic drug reactions were related with atopic family history, asthma, and allergic rhinitis diagnosis in univariate analysis.

Frequency of skin and systemic manifestations of immediate type hypersensitivity reactions caused by antibiotics and NSAIDs (85% versus 88.8% and 20% versus 44.4%, respectively) were not different from each other ($\chi^2=0.13$, $p>0.05$ and $\chi^2=2.65$, $p>0.05$ respectively).

Table 3 shows drug reactions to all drugs, antibiotics, and NSAIDs and their associations with

comorbidities of the subjects in multivariate logistic regression analysis. Taking all drug groups into consideration, family atopy, doctor-diagnosed asthma, allergic rhinitis diagnosis, and eczema were associated with hypersensitivity reactions. Drug hypersensitivity reactions to antibiotics were associated only with atopic family history and reactions to NSAIDs were associated with family atopy and ever eczema.

Table 4 shows associations between skin and systemic type hypersensitivity reactions and related factors in multivariate logistic regression analysis. Skin manifestations of immediate type drug reactions were associated with atopic family history, asthma diagnosis, allergic rhinitis diagnosis, and eczema in multivariate analysis. However, systemic type reactions were only associated with asthma diagnosis.

Table 3. Reactions to all drugs, antibiotics, and NSAIDs and their association with the characteristics of patients in multivariate logistic regression analysis

Topics	Family atopy (n=84)	Ever asthma (n=57)	Ever A. rhinitis (n= 120)	Ever eczema (n= 55)
Reaction to any drug				
OR	3.23**	2.74*	2.70*	3.80**
(95% CI)	(1.43-7.24)	(1.07-7.02)	(1.25-5.84)	(1.55-9.30)
Drug reaction to antibiotics				
OR	3.32*	2.52	2.76	
(95% CI)	(1.15-9.56)	(0.74-8.63)	(0.99-7.71)	
Drug reaction to NSAIDs				
OR	3.70*			5.88**
(95% CI)	(1.09-12.51)			(1.73-19.92)

A= Allergic, NSAIDs= Non Steroidal Anti-inflammatory Drugs.

OR= Odds Ratio, CI= Confidence Interval, *: $p<0.05$, **: $p<0.01$. Adjustment was made for age.

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Table 4. Associations between skin and systemic type hypersensitivity reactions and related factors in multivariate logistic regression analysis.

	Family atopy (n=84)	Ever asthma (n=57)	Ever A. rhinitis (n= 120)	Ever eczema (n= 55)
Skin manifestations				
OR	4.07**	3.16*	2.84*	4.59**
(95% CI)	(1.76-9.41)	(1.19-8.39)	(1.24-6.50)	(1.82-11.57)
Systemic manifestations				
OR	2.79	4.66*	2.62	
(95% CI)	(0.76-10.24)	(1.25-17.41)	(0.75-9.11)	

A= Allergic, OR= Odds Ratio, CI= Confidence Interval, *: $p<0.05$, **: $p<0.01$. Adjustment was made for age.

DISCUSSION

The present study showed the prevalence and related risk factors of immediate type drug hypersensitivity reactions in men workers. This population may represent relatively younger and healthy adult population as workers are selected after health investigation and they are examined periodically. Any type of life-time immediate type hypersensitivity reactions to drugs was reported as 3.6% in the present population. NSAIDs and antibiotics were responsible for most of the reactions in accordance with a previous population-based study.⁸ In the present study, NSAIDs and beta-lactam antibiotics consisted most of the reactions (92.7% of all hypersensitivity reactions). Most of the reactions were skin manifestations. Although the study population is relatively younger and healthier, prevalence of systemic hypersensitivity reactions was 1.3% in this population. These systemic reactions were 44.4% of all reactions for NSAIDs and 20% of all reactions for beta-lactam antibiotics.

Family history of drug allergy has been suggested as a risk factor for the patients especially with penicillin allergy⁹. The present study also showed that atopic family history was a risk factor for NSAIDs-related hypersensitivity reactions.

Previous studies reported that asthma, atopy, and chronic urticaria were risk factors for some drug reactions.¹⁰⁻¹² Multivariate regression analysis of the present study showed that all types of drug reactions to any drug were associated with family atopy, asthma diagnosis, allergic rhinitis, and eczema (Table 3). However, atopic family history seemed to be the only risk factor for beta-lactam antibiotic hypersensitivity. Besides atopic family history, ever eczema was also a risk factor for NSAIDs hypersensitivity suggesting that prior skin sensitization might be a predisposing factor

for NSAIDs-induced hypersensitivity reactions as described after exposed to aspirin and other NSAIDs in chronic urticaria patients.¹³

Drug hypersensitivity reactions are mostly presented as skin manifestations. In the present study, multivariate analysis showed that atopic family history and atopic diseases (asthma, allergic rhinitis, and eczema) were risk factors for skin manifestations of drug hypersensitivity reactions (Table 4). However, multivariate analysis showed that asthma diagnosis was the only risk factor for systemic type reactions.

We interrogated for common chronic systemic diseases, which could be related to drug reactions either by the predisposing effects of the diseases or the medications to treat the underlying disease or its complications. The present study did not show any relationship between chronic systemic diseases and drug hypersensitivity reactions. Relatively younger age and health status of the subjects might be the reason for the lack of this association because chronic metabolic diseases are manifested after the fifth decade.¹⁴ The prevalence of chronic systemic diseases in the present population was lower than general reports in the country¹⁵.

As a limitation, we did not validate the results with in-vitro or challenge tests. The study aimed to investigate prevalence self-reported drug reactions in this population. Another limitation is that there might be some unpredictable selection or recall biases that may originate from subjects. Patients may report those symptoms that they considered as important. To diminish this effect, we did not use the term 'allergy' or 'hypersensitivity' for the interviews, because most of the people in Turkey do not know the term hypersensitivity and may use the term allergy to explain any type of drug reaction including side effects. Instead, we asked for the most common and

distinguishable hypersensitivity reactions following drug intake. There may be some recall bias by the people in cross-sectional studies.

The present study was the first that demonstrated the prevalence and associated risk factors of drug hypersensitivity reactions in Turkish adult men population. Atopic family history and atopic diseases were risk factors for skin manifestations of immediate type drug hypersensitivity reactions. However, asthma diagnosis was the only risk factor for systemic immediate type drug hypersensitivity reactions. Considering that most of the hypersensitivity reactions are caused by beta-lactam antibiotics and NSAIDs, those risk groups should be followed closely with regard to use of such drugs.

Conflict of Interest

The authors have no conflict of interest regarding the manuscript.

REFERENCES

1. Miller GC, Britth HC, Valenti L. Adverse drug events in general practice patients in Australia. *Med J Aust* 2006; 184(7):321-24.
2. Volcheck GW. Clinical evaluation and management of drug hypersensitivity. *Immunol Allergy Clin N Am* 2004; 24:357-71.
3. Gomes E, Cardoso MF, Praça F, Gomes L, Marino E, Demoly P. Self-reported drug allergy in a general adult Portuguese population. *Clin Exp Allergy* 2004; 34(10):1597-601.
4. Sanchez-Borges M, Capriles-Hullet. Atopy is a risk factor for non-steroidal anti-inflammatory drug sensitivity. *Ann Allergy Asthma Immunol* 2000; 81(1):101-6
5. Pastorello EA, Zara C, Riario-Sforza GG, Pravettoni V, Incorvaia C. Atopy and intolerance of antimicrobial drugs increase the risk of reactions to acetaminophen and nimesulide in patients allergic to nonsteroidal-antiinflammatory drugs. *Allergy* 1998; 53(9):880-4.
6. Macy E, Poon KYT. Self-reported antibiotic allergy incidence and prevalence: age and sex effects. *Am J Med* 2009; 122(8):778.1-7
7. Lutomski DM, Lafollette JA, Biaglow MA, Haglund LA. Antibiotic allergies in the medical record: effect on drug selection and assessment of validity. *Pharmacotherapy* 2008; 28(11):1348-53.
8. Palma-Carlos AG, Medina G, Palma-Carlos ML. Prevalence of drug allergy in an out-patient population. *Eur Ann Allergy Clin Immunol* 2006; 38(5):142-5.
9. Apter AJ, Schelleman H, Walker A, Addya K, Rebbeck T. Clinical and genetical risk factors of self-reported penicilin allergy. *J Allergy Clin Immunol* 2008; 122(1):152-8.
10. Vervloet D, Durham S. Adverse reactions to drugs. *Br Med J* 1998; 316(7143):1511-4.
11. Borges-Sánchez M, Capriles-Hulett A. Atopy is a risk factor for nonsteroidal antiinflammatory drug sensitivity. *Ann Allergy Asthma Immunol* 2000; 84(1):101-6.
12. Sánchez-Borges M, Capriles-Hulett A, Caballero-Fonseca F. NSAID-induced urticaria and angioedema. A reappraisal of its clinical management. *Am J Clin Dermatol* 2002; 3(9):599-607.
13. Banerji A, Oren E, Hesterberg P, Hsu Y, Camargo CA, Wong JT. Ten-year study of causing of moderate to severe angioedema seen by an inpatient allergy/immunology consult service. *Allergy Asthma Proc* 2008; 29(1):88-92.
14. Arikan I, Metintas S, Kalyoncu C, Colak O, Arikan U. Evaluation of metabolic syndrome prevalence in semi-rural areas of Central Anatolia,Turkey. *Saudi Med J* 2009; 30(8):1073-80.
15. Yardim N, Mollahaliloglu S, Hulusi U, Ozbay H, Caylan AK, Unuvar N, Aydin S. Health at a Glance: Turkey 2007. Turkey: Ministry of Health of Turkey. Refik Saydam Hygiene Center, School of Public Health, Ankara 2008.