

Evaluation on the Correlation Between Gender and Drug Allergy Agent and Its Incidence Frequency

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Abstract

Background: The aim of this study was to evaluate the correlation between gender, and drug allergy agent and its incidence frequency.

Materials and Methods: The population of this retrospective study included individuals who applied to the polyclinics for any reason between 2015 and 2021 and who reported a drug allergy. The total numbers of applications, number of examinations, gender, and the presence of drug allergy and the drug allergy agent were recorded in the data form using the archive review method. Data were analyzed with the IBM SPSS V23.

Results: The total number of applications to the polyclinic was 151.036 and the number of singular patient applications was 31.915. Among 31.915 patients, 312 patients reported a drug allergy. Of these patients, 79 (25.3%) were male and 233 (74.7%) were female. The most common allergen reported was penicillin, and 58.2% of men and 45.5% of women had this allergy. No statistically significant difference was found between the distributions of allergen agents based on gender ($p > 0.096$). There was a significant difference only between Gadobutrol and gender, and a correlation was found with male gender ($p = 0.021$). No correlation was found when drug agents were divided into groups.

Conclusions: Since it has become easy to access healthcare services as well as drugs, the incidence frequency of drug allergies has also increased. Although it is predicted that gender might be effective in the occurrence of drug allergies due to hormonal and genetic differences, no correlation was found in this study. Thus, it should be noted that the risk of drug allergy incidence might exist for both genders.

Key words: Gender, drug, drug allergy.

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Introduction

Adverse drug reaction (ADR) is defined as any response to a drug that is noxious and unintended, and which occurs at doses normally used in people for prophylaxis, diagnosis, or therapy of disease by the World Health Organization. Unpredicted reactions are usually independent of the dose and unrelated to pharmacological effects of the drug and only occur in sensitive people. Unpredicted reactions are divided into subgroups as drug intolerance, hypersensitivity, and drug allergy (1).

Drug reactions similar to allergies are called drug hypersensitivity reactions (DHR) before showing the evidence of drug-specific antibodies or T cells in case of their occurrence (2). Most clinicians and patients are concerned about DHR when a new drug is started, and DHR is a significant cause of drug discontinuation (3,4,5). Due to the deficiencies and inadequacies in the diagnosis and reporting of drug allergy, the incidence of drug allergy is not known exactly. There are studies reported with a frequency ranging from 2% to 10%. A rate of 15% has been reported in hospitalized patients (2-5).

It should be stated that there might be differences due to gender in treatments in addition to drug allergies and that treatments might be made more effective with personalized treatment (6). This study was conducted to evaluate the correlation between gender, and drug allergy agent and its incidence frequency (Figure 1).



Figure 1. The correlation between gender and drug allergy (Illustrated by Yücel Özalp).

Materials and Methods

This retrospective study was conducted by evaluating the record data of the applications made to Hacettepe University Faculty of Medicine Department of Family Medicine and Sıhhiye Medico-Social Health Center polyclinic between 01.01.2015 and 01.01.2021 (6 years in total). The approval of the Hacettepe University Non-Interventional Clinical Studies Ethics Committee was obtained to conduct the study (Project no: GO.21/100, Decision no: 2021/02-40, 19.01.2021). Data of this retrospective study were obtained from the patient application recorded in the Patient Information System between 2015 and 2021. The population of the study consisted of all applications to the above mentioned polyclinics. Our polyclinics, where the study was conducted, are open to all age groups. Since it is located on the university campus, it mostly serves university staff and students. The total number of applications was 151.036 while the number of singular patient applications was 31.915. Among 31.915 patients, 312 patients reported a drug allergy. Personal information was not used in the data form. The total numbers of

applications between 01.01.2015 and 01.01.2021, numbers of examinations, gender, and the presence of drug allergy and the drug allergy agent were recorded in the data form using the archive review method. Data were analyzed with the IBM SPSS V23. The Chi-square test was used to compare the allergens based on gender. The results of the analysis were presented as frequency (percentage) and number for categorical data. The significance level was $p < 0.05$.

Results

The total number of applications to the polyclinic was 151.036 and the number of singular patient applications was 31.915. Among 31.915 patients, 312 patients reported a drug allergy. Of the patients, 79 (25.3%) were male and 233 (74.7%) were female.

The following allergens were identified among the patients; penicillin allergen in 58.2% of men and 45.5% of women, metamizole sodium in 6.3% of men and 8.2% of women, metoclopramide in 3.8% of men and 6% of women, paracetamol in 5.1% of men and 5.2% of women, diclofenac sodium in 2.5% of men and 3.4% of women, trimethoprim in 5.1% of men and 2.1% of women, sulfamoxole in 5.1% of men and 2.1% of women, naproxen sodium in 5.1% of men and 1.7% of women, clarithromycin in 3.4% of women, amoxicillin in 1.3% of men and 3% of women, vancomycin in 3.8% of men and 1.7% of women, and flurbiprofen in 1.3% of men and 2.6% of women. There was a significant difference only between Gadobutrol and gender, and a correlation was found with male gender ($p = 0.021$). The incidence percentages of other allergens in women and men and their comparisons based on gender are presented in Table 1 and Table 2 in detail.

Table 1. The distribution of allergens by gender and their statistical comparisons.

Allergen	Male	Female	Total	p
	n (%)	n (%)	n (%)	
Penicillin	46 (58.2)	106 (45.5)	152 (48.7)	0.050
Metamizole sodium	5 (6.3)	19 (8.2)	24 (7.7)	0.682
Metoclopramide	3 (3.8)	14 (6)	17 (5.4)	0.454
Paracetamol	4 (5.1)	12 (5.2)	16 (5.1)	0.515
Diclofenac sodium	2 (2.5)	8 (3.4)	10 (3.2)	0.694
Sulfamoxole +Trimethoprim	4 (5.1)	5 (2.1)	9 (2.9)	0.181
Naproxen sodium	4 (5.1)	4 (1.7)	8 (2.6)	0.104
Chlarithromycin	0 (0)	8 (3.4)	8 (2.6)	0.095
Amoxicycline	1 (1.3)	7 (3)	8 (2.6)	0.311
Vancomycin	3 (3.8)	4 (1.7)	7 (2.2)	0.281
Flurbiprofen	1 (1.3)	6 (2.6)	7 (2.2)	0.623
Moxifloxacin	0 (0)	6 (2.6)	6 (1.9)	0.189
Lohexol	1 (1.3)	5 (2.1)	6 (1.9)	0.623
Ciprofloxacin	2 (2.5)	4 (1.7)	6 (1.9)	0.649
Acetylsalicylic acid	3 (3.8)	3 (1.3)	6 (1.9)	0.447
Hyoscine butylbromide	0 (0)	5 (2.1)	5 (1.6)	0.189*
Amoxicycline+Clavunate	1 (1.3)	4 (1.7)	5 (1.6)	0,783
Cephalosporin	1 (1.3)	4 (1.7)	5 (1.6)	0.783
Vitamin B complex	0 (0)	4 (1.7)	4 (1.3)	0.241*
Lansoprazole	1 (1.3)	3 (1.3)	4 (1.3)	0.988
Gadobutrol	3 (3.8)	1 (0.4)	4 (1.3)	0.021**
Ampicillin+Sulbactam	1 (1.3)	2 (0.9)	3 (1)	0.748
Ranitidine	0 (0)	3 (1.3)	3 (1)	0.311
Metronidazole	0 (0)	3 (1.3)	3 (1)	0.311
Levofloxacin	0 (0)	3 (1.3)	3 (1)	0.311

Ibuprofen	1 (1.3)	2 (0.9)	3 (1)	0.748
Caffeine	0 (0)	3 (1.3)	3 (1)	0.560*
Thiocolchicoside	0 (0)	2 (0.9)	2 (0.6)	0.409*
Teicoplanin	0 (0)	2 (0.9)	2 (0.6)	0.409*
Sulphonamide	1 (1.3)	1 (0.4)	2 (0.6)	0.421
Pseudoephedrine	0 (0)	2 (0.9)	2 (0.6)	0.409*
Propiphenazone	0 (0)	2 (0.9)	2 (0.6)	0.409*
Prilocaine	0 (0)	2 (0.9)	2 (0.6)	0.409*
Phenytoin sodium	2 (2.5)	0 (0)	2 (0.6)	0.015*
Pheniramine maleate	0 (0)	2 (0.9)	2 (0.6)	0.409*
Pethidine hydrochloride	0 (0)	2 (0.9)	2 (0.6)	0.409*
Ofloxacin	0 (0)	2 (0.9)	2 (0.6)	0.409*
Morphine	0 (0)	2 (0.9)	2 (0.6)	0.409*
Levothyroxine sodium	0 (0)	2 (0.9)	2 (0.6)	0.409*
Ferrous glycine sulfate	0 (0)	2 (0.9)	2 (0.6)	0.409*

* The statistical analysis result of the agents that were not considered as an allergen in one of the genders was not included in the evaluation. ** The statistically significant values were written in bold.

Table 2. The distribution of allergens by gender and their statistical comparisons (Continuation of Table 1).

Allergen	Male	Female	Total	p
	n (%)	n (%)	n (%)	
Doxycycline	1 (1.3)	1 (0.4)	2 (0.6)	0.421
Ceftriaxone	1 (1.3)	1 (0.4)	2 (0.6)	0.421
Trimethobenzamide hydrochlorid	0 (0)	1 (0.4)	1 (0.3)	0.560*
Terbinafine	1 (1.3)	0 (0)	1 (0.3)	0.085*
Tenoxicam	0 (0)	1 (0.4)	1 (0.3)	0.560*
Sülfasalazine	0 (0)	1 (0.4)	1 (0.3)	0.560*
Sultamicillin tosylate	0 (0)	1 (0.4)	1 (0.3)	0.560*
Succinylated gelatin	0 (0)	1 (0.4)	1 (0.3)	0.560*
Salazopyrin	0 (0)	1 (0.4)	1 (0.3)	0.560*
Rituximab	0 (0)	1 (0.4)	1 (0.3)	0.560*
Propofol	0 (0)	1 (0.4)	1 (0.3)	0.560*
Pantoprazole	0 (0)	1 (0.4)	1 (0.3)	0.560*
Paclitaxel	0 (0)	1 (0.4)	1 (0.3)	0.560*
Ondansetron	0 (0)	1 (0.4)	1 (0.3)	0.560*
Olmesartan medoxomil	0 (0)	1 (0.4)	1 (0.3)	0.560*
Nitrofurantoin	0 (0)	1 (0.4)	1 (0.3)	0.560*
Metformin	0 (0)	1 (0.4)	1 (0.3)	0.560*
Meropenem	0 (0)	1 (0.4)	1 (0.3)	0.560*
Lercanidipine	0 (0)	1 (0.4)	1 (0.3)	0.560*
Ketamine	0 (0)	1 (0.4)	1 (0.3)	0.560*
Indomethacin	0 (0)	1 (0.4)	1 (0.3)	0.560*
Hydroxychloroquine	0 (0)	1 (0.4)	1 (0.3)	0.560*
Gabapentin	0 (0)	1 (0.4)	1 (0.3)	0.560*
Fluoxetine hydrochloride	0 (0)	1 (0.4)	1 (0.3)	0.560*
Floroquinolone	1 (1.3)	0 (0)	1 (0.3)	0.085*

Ferric hydroxide	0 (0)	1 (0.4)	1 (0.3)	0.560*
Fentanyl	0 (0)	1 (0.4)	1 (0.3)	0.560*
Etodolac	0 (0)	1 (0.4)	1 (0.3)	0.560*
Erythromycin	0 (0)	1 (0.4)	1 (0.3)	0.560*
Docetaxel	0 (0)	1 (0.4)	1 (0.3)	0.560*
Dexketoprofen trometamol	0 (0)	1 (0.4)	1 (0.3)	0.560*
Dexketoprofen	0 (0)	1 (0.4)	1 (0.3)	0.560*
Clindamycin	0 (0)	1 (0.4)	1 (0.3)	0.560*
Cimetidine	0 (0)	1 (0.4)	1 (0.3)	0.560*
Captopril	0 (0)	1 (0.4)	1 (0.3)	0.560*
Bupivacaine hydrochloride	0 (0)	1 (0.4)	1 (0.3)	0.560*
Azitromycin	0 (0)	1 (0.4)	1 (0.3)	0.560*
Acetylcysteine	0 (0)	1 (0.4)	1 (0.3)	0.560*

* The statistical analysis result of the agents that were not considered as an allergen in one of the genders was not included in the evaluation. ** The statistically significant values were written in bold.

No statistically significant difference was found between the distributions of allergen groups based on gender ($\chi^2=28.604$, $p=0.096$). Of the male patients, 58.2% had penicillin allergens, 6.3% had metamizole sodium allergens, 3.8% had metoclopramide allergens and 5.1% had paracetamol allergens. Of the female patients, 45.5% had penicillin allergens, 8.2% had metamizole sodium allergens, 6% had metoclopramide allergens and 5.2% had paracetamol allergens. Figure 2 presents the comparison of drug allergens and genders in percentages, and the allergen agents observed in less than 5 persons are presented in the “others” group.

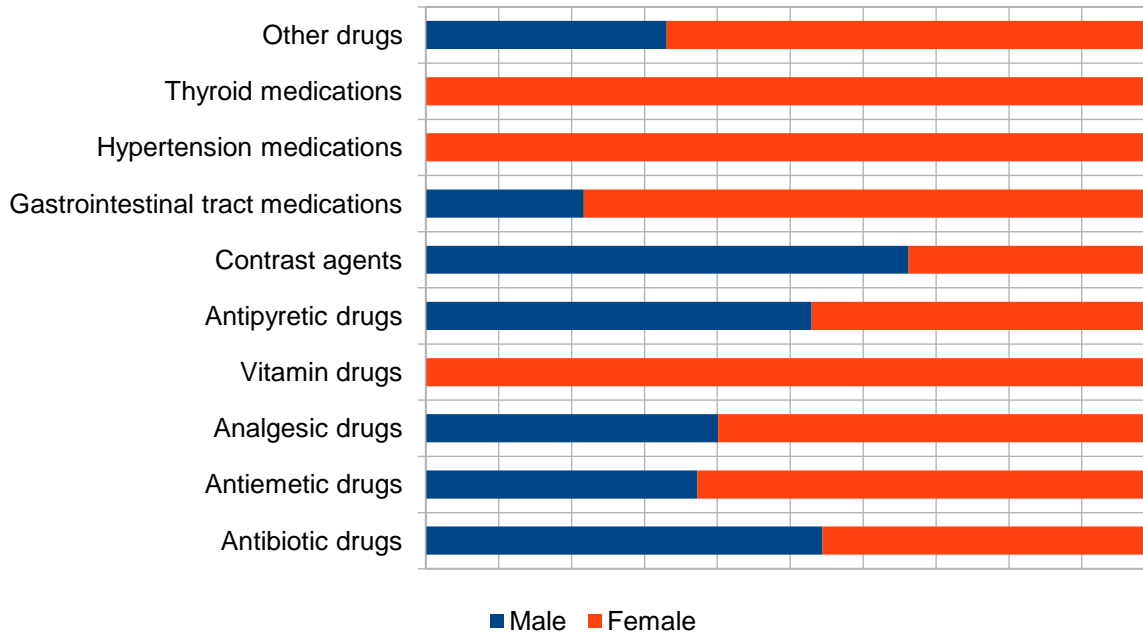


Figure 2. Comparison of the distribution of allergens by gender.

Table 3. The frequency and statistical comparisons of gender and allergen drug groups.

Allergen groups	Male	Female	Total	p
	n (%)	n (%)	n (%)	
Antibiotic drugs	57 (72.2)	141 (60.5)	198 (63.5)	0.063
Antiemetic drugs	3 (3.8)	15 (6.4)	18 (5.8)	0.384
Analgesic drugs	12 (15.2)	53 (22.7)	65 (20.8)	0.153
Vitamin drugs	0 (0)	4 (1.7)	4 (1.3)	0.241
Antipyretic drugs	5 (6.3)	13 (5.6)	18 (5.8)	0.805
Contrast agents	4 (5.1)	6 (2.6)	10 (3.2)	0.278
Gastrointestinal tract medications	1 (1.3)	11 (4.7)	12 (3.8)	0.168
Hypertension medications	0 (0)	2 (0.9)	2 (0.6)	0.409
Thyroid medications	0 (0)	2 (0.9)	2 (0.6)	0.409
Other drugs	3 (3.8)	18 (7.7)	21 (6.7)	0.229

No significant correlation was found between drug agents and gender in the analysis made by dividing drug agents into 10 separate groups. The frequency and significance values are presented in Table 3 while the comparisons of the distribution according to gender are presented in Figure 3.

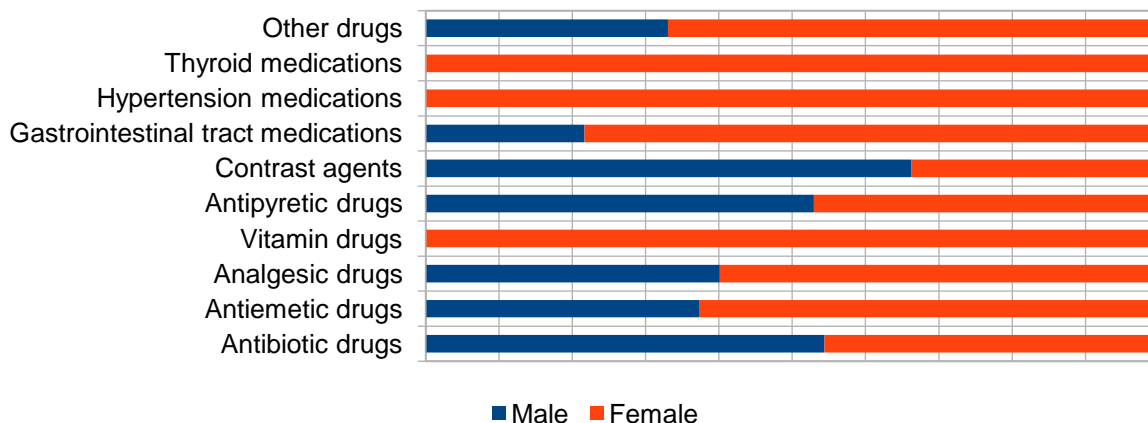


Figure 3. Comparison of the distribution of allergen drug groups by gender.

Discussion

Drug reactions have been detected more as access to healthcare services has gotten easier; thus, the number of drugs used has increased. While most of the studies on drug reactions in the literature were case reports and about the effect of one drug, the number of studies determining the frequency of drug allergies has increased after the 1990s. After it was that the incidence of fatal reactions was 0.32% and drug allergies was the fourth cause of death for inpatients in a meta-analysis compiling the studies on the incidence of drug allergy among inpatients in the United States of America, the number of relevant epidemiological studies has increased (7). It should also be remembered that mild reactions constituting a significant part of drug allergies might affect the patient's adherence to treatment and quality of life and increase the duration and cost of hospital stay for inpatients (8,9).

Most of the studies examining the frequency of drug allergies target adults; thus, the number of studies conducted with children is insufficient (10). Most of the studies conducted to determine the frequency of drug allergies among children are incidence studies. It was remarkable that these studies examined the incidence of those whose cause of application to the hospital was drug allergy and the incidence of drug allergy among children receiving treatment. In a meta-analysis by Impicciatore et al. (10) conducted to compile these studies, drug reactions were responsible for 2.09% of children who applied to the hospital, 1.46% of those who applied to a polyclinic, and 9.53% of inpatients. A study conducted to determine the prevalence of drug allergies among patients who applied to a polyclinic in a children's hospital found the prevalence of drug allergies as 10.2% (11). In a study conducted with children in Singapore, the prevalence of drug

allergies was found as 5.4% (12). The prevalence of drug allergies was 3.4% in a study conducted to examine the prevalence of asthma and allergic diseases in children aged under six (13). Furthermore, the prevalence of drug allergies was determined as 2.8% in a study conducted in the Eastern Black Sea Region (14). Advanced age is considered a risk factor for drug allergy. However, no sufficient data are supporting this among children. Since the number of child patients was low in this study, it would not be suitable to make comparisons with the studies conducted on children in the literature. A study evaluating hospital applications due to drug allergies among adults reported that the incidence of drug allergy was significantly higher in advanced ages (15). It is stated in the literature that the mean age of hospitalized children with drug allergies was significantly higher than those without drug allergies. The occurrence rate of side effects will increase in parallel with age as the usage rate of different drugs will increase. The incidence frequency of drug allergies was 0.98% in this study (312/31915). This rate is much lower than the literature data we refer to. However, this result cannot be generalized as the study population included patients who only applied to polyclinics.

It is reported in studies conducted with adults that immune and non-immune drug reactions were more common among women (16). Pouyane et al. investigated the prevalence of drug allergy as the cause of hospital application in adults and determined that women were at higher risk (15). The incidence of drug allergy was found higher among women in a study conducted in Switzerland (18). The incidence frequency was also found significantly higher among women in a study conducted in Portugal (20). Drug reactions are more common among male children in studies conducted with children. In a study conducted in Singapore, the incidence of drug allergy among hospitalized children was found significantly higher among male children (16). It was found in another study examining cases aged under 16 in Sweden that the incidence of drug allergy was significantly high between the ages of 0-4 in men, but this difference regressed in increased aged (19). However, some studies found no difference in the prevalence between genders in children. In studies conducted in Singapore and the Eastern Black Sea region, no significant difference was found in the prevalence of drug allergy between female and male children (12, 14). No statistically significant difference was found between the distributions of allergen groups according to gender in this study.

It was found in the present study that there was a significant correlation with only Gadobutrol among drug agents and male gender. Additionally, more reliable results will be obtained with an increased number of patients as the number of patients was low in this study. Although the prevalence for Gadobutrol was reported as 1.3% in other studies (21), it was 0.01% in the present study. Similarly, there were different results regarding the Gadobutrol drug allergy, which was determined to be more common among women in the same (21) and similar studies (22-24), in this study.

The fact this study was conducted with a large sample using 5-year-long data of 31915 patients including some patients who had a drug allergy but did not report it, is an important strength of this study. However, the study has some limitations. One of the most important limitations is that some patients had more than one drug allergies but the states of cross allergies of these drugs with each other were disregarded (e.g., penicillin and cephalosporins). Another important limitation is that the agents in the same drug group (e.g., moxifloxacin and ciprofloxacin in the group of quinolones) were evaluated

under different subgroups and that whether the patient was allergic to other agents in the subgroup could not be questioned due to the retrospective design.

Conclusion

A significant increase has been observed in the number of patients developing drug allergies due to the increase in the incidence frequency of drug side effects with the developments in healthcare services and provision of easy access to drugs lately. Considering the genetic and hormonal background, there is no definite opinion on the incidence and tendency of drug allergies according to gender, and the results of the current study support this opinion. Investigating the presence of the correlation between drug allergy and gender with large sample groups will provide more clear results. Furthermore, more comprehensive studies should be conducted to examine drug allergies and comorbid conditions. It is believed that the incidence frequency of drug allergies will reduce in this way.

Ethics Committee Approval: Yes

Informed Consent: NA

Peer-review: Externally peer-reviewed.

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