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RESEARCH ARTICLE

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Analysis of Patients Undergoing Metronidazole Challenge Testing: Real-Life Data

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ABSTRACT

Objective: We aimed to investigate hypersensitivity reactions in patients who underwent the metronidazole oral provocation test in the tertiary immunology and allergy clinic.

Materials and Methods: This retrospective study included patients who had a history of antibiotic hypersensitivity reactions to antibiotics other than metronidazole and underwent the metronidazole oral provocation test at an immunology and allergy clinic in a tertiary hospital between January 1, 2017 and December 31, 2023. Hypersensitivity reactions that developed during the metronidazole oral provocation test were recorded.

Results: A total of 82 patients were included in the study with 63 (76.83%) being female. The mean age of the patients was 50.14±12.47 years. A history of antibiotic hypersensitivity reactions to beta-lactams was present in 59 (71.95%) patients. During the metronidazole oral provocation test, immediate hypersensitivity reactions developed in 2 (2.43%) patients and delayed hypersensitivity reaction developed in 1 (1.21%) patient.

Conclusion: The rate of metronidazole drug hypersensitivity confirmed by the drug provocation test was found to be 3.65% in subjects with a history of hypersensitivity reactions to antibiotics other than metronidazole. Patients with a history of hypersensitivity reactions to antibiotics other than metronidazole generally tolerated metronidazole well.

Keywords: Metronidazole, drug hypersensitivity reaction, drug provocation test, beta-lactam antibiotic hypersensitivity

INTRODUCTION

Adverse drug reactions are responsible for about 3% of hospital admissions. These affect 10-20% of hospitalized patients. Drug hypersensitivity reactions (HSR) account for 20% of adverse reactions. 8% of the general population has a history of drug HSRs. Beta-lactams are the antibiotic group that are most frequently responsible for HSRs (1). Metronidazole hypersensitivity is rare and there are a limited number of case reports in the literature (2). Metronidazole is a bactericidal antimicrobial agent from the nitroimidazole antibiotics. It is one of the primary treatments for anaerobic infections. It is also used in the treatment of protozoal infections, Clostridium difficile, gastrointestinal tract infections due to Helicobacter pylori, bacterial vaginosis, Trichomoniasis vaginalis, giardiasis and amebiasis (2). Immediate and delayed HSRs to metronidazole have been reported. There is a wide range of IgE-mediated HSRs, ranging from pruritus and angioedema to anaphylaxis (3-5). Delayed HSRs such as fixed drug eruption, Steven Johnson Syndrome/Toxic Epidermal Necrolysis, acute generalized exanthematous pustulosis, and symmetrical drug-related intertriginous and flexural exanthema are also observed (6-9). Allergic contact dermatitis may develop due to the topical use of metronidazole (10,11).

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In this study, we aimed to examine HSRs in patients who underwent the metronidazole oral provocation test (OPT) in the immunology and allergy clinic.

MATERIALS and METHODS

Research Method and Ethics Committee Approval

This retrospective study was carried out at the immunology and allergy clinic in a tertiary hospital. Ethical approval was obtained from the local ethics committee (February 14, 2024-BÇEK/20). The study was carried out according to the ethical standards stated in the Declaration of Helsinki and its amendments, and all patients were examined and included with respect to good clinical practice guidelines.

Patient Population

The study population consisted of adults who had presented to our allergy clinic between January 1, 2017, and December 31, 2023, with a history of HSRs to antibiotics other than metronidazole, and underwent metronidazole OPTs, for whom records were accessible. Patients who described HSRs to metronidazole were excluded from the study.

Data Collection

Demographic and clinical characteristics of the patients and the results of metronidazole OPTs were recorded by reviewing the patient records. Drug HSRs that occurred in the patients were documented. The HSRs were categorized as immediate or delayed HSRs. Also, the patients' age, gender, history of asthma, atopy status, history of drug allergy, history of food allergy, and history of bee venom allergy were recorded. The results of skin prick tests and allergen-specific IgE tests for aeroallergens were evaluated. Presence of atopy was considered positive if any of these were positive.

Drug Provocation Test

Metronidazole OPT was performed on the patients who had no contraindications for the drug provocation test. The test was conducted in a controlled environment where necessary medical equipment for intervention in case an allergic reaction occurred. Precautionary measures for intervention in case of an allergic reaction were taken. Drugs that could potentially mask or exacerbate reactions during the test were identified. These drugs were stopped before the tests, based on consultations with the relevant clinics. The test was performed at least 4 weeks after a recent HSR. Due to the wide range availability of alternative antibiotics to the antibiotics that previously caused reactions in the included patients and the absence of suspicion of allergic reactions in their histories, diagnostic tests were not planned. Additionally, all patients included in the study had a history of immediate HSRs with antibiotics. Therefore, patch testing was not performed on the patients. Informed consents were obtained from the patients before the OPTs. The OPTs were conducted as single-blind, placebo-controlled trials. The tests were conducted in two steps. In the first step, 125 mg of metronidazole was administered, followed by 375 mg in the second step, for a total of 500 mg of metronidazole. At least 60 minutes were allowed between the doses. The patients were closely monitored for potential HSRs. The patients undergoing the tests were observed for a total of 8 hours on the test day and were re-evaluated for the signs and symptoms of allergic reactions 24 hours later. The metronidazole OPT procedure, evaluation of the HSRs that occurred during the test, and management of these reactions were performed in accordance with the European Network for Drug Allergy (ENDA) Guidelines and International Consensus on drug allergy (ICON) (12, 13).

Definitions

HSRs were evaluated as immediate and delayed HSRs in accordance with the international consensus report (12). Urticaria, angioedema, rhinitis, bronchospasm, and gastrointestinal symptoms (nausea-vomiting, diarrhea, abdominal pain) that developed in the first 6 hours after the drug dose were considered as immediate HSRs. Symptoms starting after the initial 6 hours were classified as delayed HSRs.

Statistical Analysis

The I.B.M. SPSS Inc. 25.0 for Windows, Chicago, IL, USA program was used to analyze the data. Continuous variables are shown as mean±standard deviation and categorical variables as numbers (%).

RESULTS

A total of 82 patients were included in the study with 63 (76.83%) being female. The mean age of the patients was 50.14±12.47 years. An asthma diagnosis was present in 18 (21.95%), atopy in 9 (10.97%), food allergy in

2 (2.43%), and bee venom allergy in 1 (1.21%) out of 82 patients. While 37 (45.12%) patients had a history of HSRs to a single antibiotic group, 45 (54.48%) patients had a history of HSRs to two or more antibiotic groups. Fifty-nine (71.95%), 23 (28.04%), and 17 (20.73%) of the patients, had a history of HSRs to beta-lactam, quinolone, and macrolide antibiotics, respectively. The demographic and clinical characteristics of the patients are presented in Table I. During the metronidazole OPT, 2 (2.43%) patients experienced immediate HSRs and 1 (1.21%) patient experienced delayed HSR. The characteristics of the patients who experienced HSRs are demonstrated in Table II.

DISCUSSION

Metronidazole is frequently prescribed to treat anaerobic infections as well as Helicobacter pylori (14, 15). The only effective antibiotics in the curative treatment of trichomoniasis are nitroimidazole antibiotics, including metronidazole (16). However, metronidazole hypersensitivity is less common than with other antibiotics (2). Although there is limited literature on the prevalence of metronidazole hypersensitivity, a study in which more than 1 million patient records of inpatients and outpatients treated in a tertiary hospital between 2010 and 2018 were examined found that 25,062 patients had a history of beta-lactam hypersensitivity, while the number of patients with

Table I: Demographic and Clinical Characteristics of the Patients (n=82).

Age	50.14±12.47 (24-75)
Gender, n (%)	
Male	19 (23.17)
Female	63 (76.83)
Comorbidities, n (%)	
Presence of Concomitant Asthma Diagnosis	18 (21.95)
Atopy	
Yes	9 (10.97)
No	26 (31.70)
Unknown	47 (57.31)
Food Allergy, n (%)	2 (2.43)
Bee Venom Allergy, n (%)	1 (1.21)
History of HSRs to Antibiotics, n (%)	
Single Antibiotic Group	53 (64.63)
Two or More Different Antibiotic Groups	29 (35.36)
Beta-Lactams	59 (71.95)
Quinolones	23 (28.04)
Macrolides	17 (20.73)
HSRs Occurring During Metronidazole OPT, n (%)	
Immediate HSRs	2 (2.43)
Delayed HSRs	1 (1.21)

HSR: Hypersensitivity Reaction, **OPT:** Oral Provocation Test

Table II: Characteristics of Patients Experiencing Metronidazole Hypersensitivity Reaction (n=3).

Parameters	Patient 1	Patient 2	Patient 3
Age	52	67	55
Gender	Female	Female	Female
Asthma	No	No	No
Atopy	Unknown	Yes	No
Food Allergy	No	No	No
Bee Allergy	No	No	No
History of HSRs to Antibiotics	Beta-Lactam	Beta-Lactam	Beta-Lactam, Macrolide
History of HSRs to Drugs Other than Antibiotics	Methimazole, Acetylsalicylic Acid	No	Lansoprazole
Metronidazole OPT			
Type of HSR	Immediate	Delayed	Immediate
Symptoms During The HSR			
Itching-Erythema	-	-	+
Urticaria	-	+	
Angioedema	-	-	+
Dyspnea	+	-	+
Time of Onset of HSRs (Minutes)	60	780	300

HSR: Hypersensitivity Reaction, **OPT:** Oral Provocation Test

imidazole group antibiotic hypersensitivity label were 38 (<0.01%) (17). In a study examining antibiotic hypersensitivity records in outpatients between 2012 and 2021, a history of metronidazole hypersensitivity was found in 3.6% of the patients. These patients were re-evaluated and drug skin tests were performed, and skin test positivity was detected in 11.1% of the patients with a history of metronidazole hypersensitivity. In addition, 1 patient had a history of anaphylaxis (18). In a study in which the records of patients with drug hypersensitivity between 2007 and 2019 were analyzed and then allergic evaluation was performed on these patients, a history of metronidazole hypersensitivity was found in only 6 patients and hypersensitivity was proven in half of these patients (19). In a study of 10 years of drug-related anaphylaxis records in China, it was reported that metronidazole caused anaphylaxis in only 1 patient (20). In our study, HSRs developed in only 3 (3.65%) patients who underwent metronidazole OPT and all the HSRs were mild.

In our study, 76.83% of the patients were female and all of the patients who experienced HSRs during the test were women. The prevalence of immediate and delayed drug hypersensitivity is higher in women than in men. Studies have shown that the prevalence of patients reporting drug allergies is higher in women. The antibiotic allergy label affects women more. This affects their choice of antibiotics and most patients who seek relief from the label of antibiotic allergy are women (21). According to a cohort study using drug allergy registries in the USA, penicillin was the most commonly reported drug that caused HSR and 74% of the patients who reported drug hypersensitivities were women (22). In a study of patients admitted to a tertiary hospital between 2010-2018, it was found that women had more antibiotic allergy labels than men and 68% of patients with antibiotic allergy labels against at least 1 antibiotic were women (17). In addition, in a retrospective study of drug provocation tests performed in patients with a history of HSRs to antibiotics, HSRs during provocation tests developed more frequently in women (23). A history of drug and antibiotic hypersensitivity is clearly more common in women than in men. However, the reason for this is complex and multifactorial. Abnormal X chromosome inactivation in women is thought to lead to an increased risk of autoimmunity. In addition, hormonal factors may affect regulatory T lymphocyte functions and lead to autoimmune and allergic diseases. Also, the fact that women use the healthcare system more than men, that all drug groups, especially psychotropic drugs and antibiotics, are prescribed more frequently to women, and that women pay more for examinations and diagnostic tests may play a role in the higher drug allergy labeling in women. The higher level of anxiety in women may contribute to this situation by increasing awareness of drug intolerance. The fact that autoimmune diseases and diseases such as urticaria are more common in women may lead to symptoms of these diseases being mistakenly perceived as drug hypersensitivity (21).

In our study, 71.95% of the patients had a history of beta-lactam hypersensitivity. Also, all patients who experienced HSRs during OPTs had a history of beta-lactam hypersensitivity. There was a history of quinolone hypersensitivity in 28.04% and macrolide hypersensitivity in 20.73% of the patients. In studies investigating the drug hypersensitivity history of patients, antibiotic hypersensitivity was the most frequently reported drug hypersensitivity and beta-lactam hypersensitivity was the most frequently reported antibiotic hypersensitivity. Beta-lactam hypersensitivity was followed by quinolone and macrolide hypersensitivity, respectively (17, 18, 22, 24, 25). In a study in which patients with a history of drug hypersensitivity were examined and allergic evaluation was performed, it was found that beta-lactams constituted the majority of proven antibiotic hypersensitivity (19).

There are some limitations to our study. The most important limitation is that the study was retrospective, and therefore, diagnostic tests for drugs responsible for HSRs were not performed in the patients included in our study. Again, since it was a retrospective study, only the patients' file data were evaluated. The existence of a wide range of alternative antibiotic groups, the lack of diagnostic test kits for beta-lactam antibiotics, and ethical issues such as the risk of potentially life-threatening reactions during diagnostic testing may be the reason for the limitation in the file information. Another limitation is that our study was conducted in a relatively small population due to its single-center nature. However, although our study was a retrospective and single-center study including 82 patients, we believe that it will provide valuable insights on this subject, considering that the literature on this subject mostly consists of case reports.

In conclusion, our study is one of the rare studies conducted on this subject and is the first data in our country. In our clinic, the rate of metronidazole hypersensitivity

confirmed by OPT was found to be 3.65% and reactions were mild in patients with a history of HSRs to antibiotics other than metronidazole. Patients with a history of HSRs to antibiotics other than metronidazole generally tolerate metronidazole well. Large-scale, multi-center research with broader patient populations would enhance our understanding of metronidazole HSRs in individuals with history of confirmed antibiotic hypersensitivity.

Conflict of Interest

All authors declare that no conflict of interest may have influenced either the conduct or the presentation of the research.

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Informed Consent

Ethical approval was acquired from the local ethics committee (February 14th 2024/2024-BÇEK/20). The study was carried out according to the ethical standards stated in the Declaration of Helsinki and its amendments, and all patients were examined and included with respect to good clinical practice guidelines.

Authorship Contributions

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