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Oral Provocation with Alternative Medicine in H1-Antihistamine Drug Allergies

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ABSTRACT

Objective: There is currently a lack of comprehensive studies that provide clear information about the frequency and characteristics of hypersensitivity reactions associated with H1 antihistamines. The aim of our study was to evaluate the subjects with antihistamine drug allergy diagnosed in our clinic and the provocation tests performed on them with alternative agents.

Materials and Methods: This retrospective study was carried out at the immunology and allergy clinic in a tertiary hospital. The study population consisted of adults who presented to our allergy clinic between January 1, 2017 and December 31, 2023 with a history of H1 antihistamine drug allergy and underwent alternative H1 antihistamine drug provocation tests, for whom records were accessible.

Results: A total of 45 patients were included in the study. The mean age of the patients was 39.75 ± 13.30 years with 34 (75.55%) being female. Regarding the initial allergic reaction history to H1 antihistamine drugs, allergic reactions occurred with pheniramine hydrogen maleate in 17 (37.77%), with levocetirizine dihydrochloride in 9 (20%), with desloratadine in 7 (15.55%), with cetirizine dihydrochloride in 6 (13.33%), with bilastine in 6 (13.33%), with rupatadine fumarate in 3 (6.66%) patients, and with fexofenadine hydrochloride 1 patient (2.22%). Allergic reactions developed in 7 (15.55%) patients during oral provocation tests.

Conclusion: In conclusion, caution is advised with H1 antihistamine hypersensitivity. Misinterpreting hypersensitivity symptoms as those of the primary allergic condition may lead to treatment delays or unnecessary escalation, potentially resulting in life-threatening reactions. Additionally, further research is needed to clarify which antihistamines pose higher allergic risks and to guide the selection of alternatives for testing.

Keywords: H1 antihistamines, hypersensitivity reaction, drug provocation test

INTRODUCTION

H1-antihistamines function as reversible competitive antagonists of the H1-histamine receptor and prevent binding of histamine to the receptors. Oral H1-antihistamines are classified into first and second generations. H1-antihistamines are widely used in the treatment of a variety of conditions such as urticaria, eczema, allergic reactions, and allergic rhinitis (1).

Although their use is for anti-allergic purposes, cases of hypersensitivity reactions resulting from the use of antihistamine drugs have been reported. Reported clinical presentations include allergic contact dermatitis, delayed hypersensitivity reactions like fixed drug eruption (FDE), as well as manifestations associated with IgE-mediated reactions such as urticaria and even anaphylaxis (2-6).It is important to identify adverse reactions to H1 antihistamines, as evident drug allergy may be interpreted as non-response of the allergic disease that gave rise to the treatment indication otherwise. Recognizing the causal relationship between the patient's clinic and the drug-induced hypersensitivity reaction is often challenging and

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requires suspicion. When a reaction occurs to an antihistamine preparation of one class, it is likely, but not always, to occur to other members of the same class. Diagnosis, as in all drug allergies, can be confirmed by a provocation test (2).

The aim of our study was to evaluate the subjects with antihistamine drug allergy diagnosed in our clinic and the provocation tests performed on them with alternative agents.

MATERIALS and METHODS

Study Design, Setting and Population

This retrospective study was carried out at the immunology and allergy clinic in a tertiary hospital. The study population consisted of adults who presented to our allergy clinic between January 1, 2017, and December 31, 2023, with a history of H1 antihistamine drug allergy and underwent alternative H1 antihistamine drug provocation tests, for whom records were accessible. The results of oral provocation tests (OPT) conducted to find alternative safe H1 antihistamine drugs for patients presenting with a history of H1 antihistamine drug allergy to our clinic were analyzed.

Ethical Considerations

Ethical approval was acquired from the local ethics committee (February 14th2024/BÇEK-2024/20). 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.

Data Collection

Demographic and clinical information of the patients, as well as information regarding the results of H1 antihistamine provocation tests, were recorded by reviewing patient records. Drug hypersensitivity reactions that occurred in the patients were documented. The type of hypersensitivity reaction was categorized as early-onset or delayed-onset. Additionally, patient data including age, gender, presence of asthma diagnosis, atopy, history of drug allergy, food allergy and bee venom allergy were recorded. The results of skin prick tests conducted on patients were examined. The presence of atopy was considered positive if any of these tests were positive.

Procedures During the Drug Provocation Test and Selection of Alternative Drugs for the Test

During the drug provocation test with H1 antihistamines, the following procedures were followed: The test was conducted in a controlled environment where necessary medical equipment for intervention in case of an allergic reaction was available. Patients without contraindications for drug provocation tests were selected for the procedure. Precautionary measures for intervention in case of an allergic reaction were taken. Drug groups that could potentially mask or exacerbate reactions during the test were identified. Discussions were held with relevant departments based on recommended durations to discontinue these drug groups to prevent interference with or exacerbation of the reaction during the test (7-9). The test was conducted at least 4 weeks after the patient's most recent allergic reaction history. Due to the availability of alternatives to drugs that previously caused reactions in the included patients and the absence of suspicion of allergic reactions in their histories, diagnostic tests were not planned. Oral provocation tests with alternative H1 antihistamine drugs were performed. Additionally, all patients included in the study had early-onset allergic reactions consistent with previous reactions to H1 antihistamine drugs. Therefore, patch testing was not performed on the patients. The oral provocation tests were conducted as single-blind, placebo-controlled trials. The provocation test started orally with a low dose (one-quarter of the effective dose for each alternative drug) and was carried out in two steps, with the total dose administered accordingly. A minimum of 60 minutes was allowed between the two doses. Patients were closely monitored for potential hypersensitivity reactions. Patients undergoing the test were observed for a total of 8 hours on the test day and were re-evaluated for signs and symptoms of allergic reactions 24 hours later. The evaluation of hypersensitivity reactions occurring after the test and the management of reactions were performed according to the ENDA Guidelines and ICON (10-11).

Definitions

The reactions that developed in patients undergoing provocation tests were evaluated according to international consensus reports as early-onset and delayed-onset hypersensitivity reactions (11). Urticaria, angioedema, rhinitis, bronchospasm, and gastrointestinal symptoms

(nausea-vomiting, diarrhea, abdominal pain) that developed within the first 6 hours after drug administration were considered early-onset hypersensitivity reactions. Symptoms starting after the initial 6 hours were classified as delayed-onset hypersensitivity reactions.

Multiple drug allergy is defined as the development of hypersensitivity reactions to at least two different drug groups (12).

Statistical Analysis

SPSS 25 for Windows software was used for data analysis. Continuous variables are presented as mean ± standard deviation, and categorical variables are shown as number and percentages.

RESULTS

A total of 45 patients were included in the study. The mean age of the patients was 39.75 ± 13.30 years with 34 (75.55%) females. Regarding the initial allergic reaction history to H1 antihistamine drugs, allergic reactions occurred with pheniramine hydrogen maleate in 17 (37.77%), levocetirizine dihydrochloride in 9 (20%), desloratadine in 7 (15.55%), cetirizine dihydrochloride in 6 (13.33%), bilastine in 6 (13.33%), rupatadine fumarate in 3 (6.66%) patients and fexofenadine hydrochloride 1 patient (2.22%). The history of allergic reactions to non-H1 antihistamine drugs in the study patients revealed that 11 of 45 patients (24.44%) had a history of allergic reactions only to H1 antihistamine drugs, and 34 (75.55%) had a history of multidrug allergy. Among the patients, the most common drug allergy associated with H1 antihistamine allergy was with nonsteroidal anti-inflammatory drugs, and such allergies were seen in 21 patients (46.66%). Asthma diagnosis was present in 7 (15.55%), perennial atopy in 6 (13.33%), seasonal atopy in 3 (6.66%), and bee venom allergy in 2 (4.44%) out of 45 patients. None of the patients included in the study had concomitant food allergies (Table I).

Table I: Demographic and Clinical Characteristics of the Patients (n=45).

Age (mean ± SD)	39.75 ± 13.30
Gender	
Male	11 (24.44)
Female	34 (75.55)
First allergic reaction that developed to H1 antihistamines	
Pheniramine hydrogen maleate	17 (37.77)
Levocetirizine dihydrochloride	9 (20)
Cetirizine dihydrochloride	6 (13.33)
Desloratadine	7 (15.55)
Rupatadine fumarate	3 (6.66)
Bilastine	6 (13.33)
Fexofenadine hydrochloride	1 (2.22)
Distribution of H1 antihistamines used for OPT	
Pheniramine hydrogen maleate	3 (6.66)
Levocetirizine dihydrochloride	12 (26.66)
Cetirizine dihydrochloride	2 (4.44)
Desloratadine	5 (11.11)
Rupatadine fumarate	6 (13.33)
Bilastine	14 (31.11)
Fexofenadine hydrochloride	2 (4.44)
Loratadine	1 (2.22)
Number of reactions that developed during OPT	7 (15.55)
Type of reaction that developed during OPT	
Early	6 (85.71)
Late	1 (14.28)
Presence of concomitant asthma diagnosis	7 (15.55)
Atopy	9 (19.99)
Perennial atopy	6 (13.33)
Seasonal atopy	3 (6.66)
Unknown	3 (6.66)
History of non-H1 antihistamine drug allergy	34 (75.55)
NSAID allergy	21 (46.66)
Corticosteroid allergy	7 (15.55)
Local anesthetic allergy	4 (8.88)
PPI allergy	6 (13.33)
Antibiotic allergy	6 (13.33)
Other drug allergies	5 (11.11)

Data are expressed as number (percentage) unless otherwise stated. **NSAID:** Non-steroidal anti-inflammatory drug, **OPT:** Oral provocation test, **PPI:** Proton pump inhibitor, **SD:** Standard deviation

An oral provocation test (OPT) with an H1 antihistamine different from the drugs to which they had previously reacted were performed to find alternative treatments. Fourteen (31.11%) patients underwent OPT with bilastine, 12 (26.66%) levocetirizine dihydrochloride, 6 (13.33%) rupatadine fumarate, 5 (11.11%) desloratadine, 3 (6.66%) pheniramine hydrogen maleate, 2 (4.44%) cetirizine dihydrochloride, 2 (4.44%) fexofenadine hydrochloride, and 1 (2.22%) loratadine. Allergic reactions developed in 7 (15.55%) patients during OPT. OPT was applied to 3 of these patients with levocetirizine dihydrochloride, to 2 with bilastine, and to 1 with desloratadine and pheniramine hydrogen maleate. During OPT, 6 patients experienced early hypersensitivity reactions, while 1 patient

developed a delayed-type hypersensitivity reaction. Laryngeal edema, bronchospasm, hypotension, gastrointestinal system symptoms and cardiac arrest were not observed in the patients during OPT. The characteristics of patients who developed allergic reactions during OPT is demonstrated in Table II.

DISCUSSION

H1 antihistamines are commonly used in the treatment of allergic diseases and are also indicated, either as monotherapy or in combination, for non-allergic conditions such as itching, the common cold, and the flu. Studies have demonstrated the effectiveness and safety of these drugs in allergic patients (13). Although the observation of hypersensitivity reactions with this group of drugs may seem surprising considering their mechanism of action, such cases are seen in clinical practice. Clinical presentations such as allergic contact dermatitis, FDE, urticaria and even anaphylaxis have been reported (2-6).Yet there is currently no comprehensive study providing clear information about the frequency and characteristics of hypersensitivity reactions associated with H1 antihistamines. With the present study the 7-year data from our clinic were reviewed and discussed.

Among the H1 antihistamines, there is no active ingredient that has been proven to be more responsible for hypersensitivity reactions so far, and there is no definitive evidence yet to guide the selection of an alternative H1 antihistamine to perform OPT. A study analyzing antihistamine allergies reported between 1949 and 2013 showed that hypersensitivity reactions could develop with drugs in all antihistamine classes, but most frequently with piperazine, followed by piperidine groups. The most frequently responsible agent in these groups was cetirizine, followed by hydroxyzine (2). In our study, the responsible agent for H1 antihistamine allergy in 37.77% of the patients was found to be pheniramine hydrogen maleate, followed by levocetirizine dihydrochloride, and cetirizine.

Another noteworthy aspect of our data analysis is that 75.55% of patients presenting with H1 antihistamine allergy had multiple drug allergies, and the most commonly

Table II: Characteristics of patients who developed allergic reactions during oral provocation testing.

Parameters	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7
Age	53	65	38	27	67	28	49
Gender	Female	Female	Male	Female	Male	Male	Male
Drug that previously caused an allergy	Desloratadine	Rupatadin Bilastine	Levocetirizine	Levocetirizine	Bilastine	Pheniramine	Levocetirizine Bilastine
Alternative antihistamine used for OPT	Levocetirizine	Levocetirizine	Pheniramine	Bilastine	Levocetirizine	Bilastine	Desloratadine
Type of reaction that developed	Early	Early	Early	Late	Early	Early	Early
Time of onset of reaction (minutes)	120	120	15	900	60	50	300
Symptoms that developed during the reaction							
Itching-Erythema	+	+	+	+	+	-	+
Urticaria	-	-	+	+	-	-	+
Angioedema	-	-	-	-	+	-	-
Dyspnea	-	-	-	-	-	+	-
History of non-H1 antihistamine drug allergy	+	-	+	+	+	+	-
NSAID	-	-	+	+	+	-	-
Corticosteroid	-	-	-	-	-	+	-
Local anesthetic	-	-	-	-	-	-	-
PPI	-	-	-	-	-	+	-
Antibiotic	-	-	-	-	-	-	-
Other drugs	+	-	-	-	-	-	-

NSAID: Non-steroidal anti-inflammatory drug; **OPT:** Oral provocation test; **PPI:** Proton pump inhibitor

associated drug allergy group with antihistamine allergy was NSAIDs. The literature contains rare case reports and some insights related to this topic. In a COX screening assay using ovine COX-1/COX-2, loratadine was observed to inhibit COX-1 activity at low concentrations, whereas fexofenadine preferentially inhibited COX-2 activity when compared to a known investigational highly selective COX-2 inhibitor (14). Based on these findings, it has been suggested that concurrent NSAID sensitivity in a patient with H1 antihistamine-induced urticaria may be the result of a common pathogenic mechanism (15). Furthermore, two separate cases have been reported where chlorpheniramine hypersensitivity occurred alongside aspirin intolerance (16,17). Although it is a rarely reported condition, there was a high incidence of co-occurrence of antihistamine allergy with NSAID allergy in our study. The high prevalence of NSAID drug allergies and the fact that antihistamines are commonly used as the first-line drugs in the treatment of allergic reactions associated with these drugs raise concerns about potential safety issues.

It has been suggested that the development of hypersensitivity reactions to antihistamine drugs may be attributed to several factors, including molecular similarity to histamine, haptenization of drug metabolites, formation of abnormal metabolic pathways, and reactions originating from side chains in the drug molecule (5,18,19). Although there is no consensus on the choice of alternative antihistamines for OPT, it is appropriate to use an antihistamine from a different class than the drug causing the reaction (2). However, it is possible for allergic reactions to occur during the OPT with the use of different groups of antihistamines (3,18). In our study, although OPT was administered to all patients with an antihistamine from a different group than the responsible agent, hypersensitivity developed in 7 patients.

Both early-onset and delayed-onset allergic reactions such as urticaria/angioedema, contact dermatitis, anaphylaxis, and FDE have been reported with H1 antihistamines. Urticaria, either alone or in conjunction with angioedema, is the most commonly reported symptom (2). During OPT to find alternative antihistamine, 42.85% of the patients had urticaria, 71.42% had itching and erythema without urticaria, and 85.71% had symptoms consistent with early-onset allergic reactions. Only one patient developed a delayed-onset allergic reaction, experiencing widespread itching and erythema approximately 15 hours after OPT. One patient had isolated angioedema, while the other had only shortness of breath. In patients who developed reactions during alternative drug OPT, laryngeal edema, bronchospasm, hypotension, gastrointestinal symptoms, or cardiac arrest were not observed, and there was no need for adrenaline administration.

In the data we reviewed, allergic reactions developed in 1 patient among the 3 patients who underwent OPT with pheniramine hydrogen maleate. Similarly, allergic reactions occurred in 3 patients among the 12 patients who underwent oral provocation testing with levocetirizine dihydrochloride. Although the number of included patients was limited, pheniramine hydrogen maleate and levocetirizine dihydrochloride ranked prominently both in the initial reactions of the patients and during OPT when the distribution of reactions was analyzed according to the agent. This suggests that these two agents cause hypersensitivity reactions more frequently compared to other H1 antihistamines. This relatively high rate may be due to the fact that pheniramine hydrogen maleate is available in both oral and intravenous forms and is frequently preferred in emergency departments and daily use. The history of allergic reactions with rupatadine fumarate in the present study is relatively low, and no allergic reactions were observed in OPTs performed with this agent. Considering the limited number of reports of rupatadine-related reactions in the literature compared to other preparations, it is reasonable to speculate that the risk of allergic reactions with rupatadine fumarate may be lower. However, due to the limited number of patients in our study, it is not possible to reach such a conclusion at this stage.

The main limitation of the study is the limited number of patients due to the rarity of allergic reactions to antihistamines, as well as the retrospective nature of the study, which limited access to additional data. Performing OPT using commercially available drug formulations presents another limitation of our study, as it does not allow us to exclude potential hypersensitivity reactions to the excipients contained in these medications. Additionally, the question may arise as to why diagnostic testing was not conducted with the drug that had a history of causing the initial reaction in patients. However, due to the retrospective nature of our study, existing medical records and hospital system data were evaluated. We hypothesize that the reasons for not conducting diagnostic tests may include the availability of alternative preparations and the ethical concerns surrounding potential reactions that could occur during these tests. When interpreting the results, it

is important to consider that this is a single-center, retrospective study involving 45 patients. Considering that the literature generally consists of case reports with a much smaller number of patients, we believe our study sheds light on this issue.

In conclusion, caution should be exercised regarding H1 antihistamine hypersensitivity. If hypersensitivity symptoms related to antihistamine use is mistaken for symptoms of the primary allergic disease, treatment may be delayed, and may be planeed as unnecessary escalation of the treatment with higher doses, even resulting in life-threatening hypersensitivity reactions. Furthermore, we believe that there is a group of drug allergies deserving of new and comprehensive research, which includes uncertainties and questions regarding which antihistamines carry a higher risk of allergic reactions and the selection of alternative medications for testing purposes.

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No funding was received for the study.

Conflict of interests

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

Ethical approval

Ethical approval was acquired from the local ethics committee (February 14th2024/BÇEK-2024/20). 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.

Data Availability

The data set used and/or analyzed during the present study is available upon reasonable request.

Authorship Contributions

Concept: **Kurtulus Aksu,** Design: **Hatice Celik Tuglu, Kurtulus Aksu, Melis Yagdıran, Fatma Dindar Celik, Ozgur Akkal, Onur Telli, Gurgun Tugce Vural Solak,** Data collection or processing: **Hatice Celik Tuglu,** Analysis or Interpretation: **Hatice Celik Tuglu,** Literature search: **Hatice Celik Tuglu, Kurtulus Aksu, Melis Yagdıran, Fatma Dindar Celik, Ozgur Akkal, Onur Telli, Gurgun Tugce Vural Solak,** Writing: **Hatice Celik Tuglu, Kurtulus Aksu,** Approval: **Hatice Celik Tuglu, Kurtulus Aksu, Melis Yagdıran, Fatma Dindar Celik, Ozgur Akkal, Onur Telli, Gurgun Tugce Vural Solak.**

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