This article can be cited as: Sarafan N, Alipour A, Shariati A. Drug-induced oral lichenoid reactions in patients consuming antihypertensive drugs. Cardiovasc Biomed J. 2022; 2(2): 3 -10.

Original Article

Drug-induced oral lichenoid reactions in patients consuming antihypertensive drugs

Negar Sarafan [1], ***Afra Alipour*** [1], ***Akram Shariati*** [2,*]

[1] Department of Oral and Maxillofacial School of Dentistry, Urmia University of Medical Sciences, Urmia, Iran
[2] Department of Cardiology, School of Medicine, Urmia University of Medical Sciences, Urmia, Iran

*** Corresponding Author:**
Address: 17 Shahrivar Street, Seyed Al Shohada Heart Center, Urmia, Iran. **Postal code:** 5718749441; **Tel:** +98 44325909; **Email:** Shariatiakram2016@gmail.com.

Article Information:
Received: 26 Nov 2022; Revised: 16 Feb 2023; Accepted: 04 Mar 2023 DOI: 10.18502/cbj.v2i2.12155

Abstract

Objectives: High blood pressure (HBP) is a persistent and widespread condition, and increasing numbers of patients are taking medication to reduce HBP symptoms and control blood pressure. Patients taking specific antihypertensive medications have been reported to experience oral lichenoid reactions. Various antihypertensive drugs have entered the market, and it is essential to study how they may affect the occurrence of oral lichenoid reactions. This study aimed at assessing the frequency of drug-induced oral lichenoid responses in patients receiving antihypertensive medications.

Methods: Four hundred fifty patients who took hypertension medications referring to Seyed al-Shohdai Hospital in Urmia in 2021 were the subject of this cross-sectional study. After the patient's first visit to the hospital, a thorough medical history was obtained from them. The type, dose, and duration of antihypertensive medications taken at the study's time were questioned and documented together with demographic data. The diagnosis of the oral lichenoid reactions was then made by examining the patients. Chi-square and Spearman's correlation tests were used in SPSS version 26 to evaluate the data.

Results: Oral lichenoid reaction was observed in about 3.3% of patients. The average age of patients who showed oral lichenoid reaction was 53.7 ± 7.1, they had taken medicine for an average of 1 to 30 months, and 66.7% were female.

Conclusions: Patients taking antihypertensive drugs, e.g., hydrochlorothiazide, methyldopa, metoprolol, and propranolol, should be examined and followed up regarding oral lichenoid reactions.

Keywords: Hypertension, antihypertensive drugs, Oral Lichenoid Reaction

Introduction

Hypertension is one of the most prevalent Cardiovascular diseases (CVDs), with an adult incidence of 20% to 30% in wealthy nations and a prevalence of 2-5% in children and adolescents (1,2). Antihypertensive medications are an efficient therapeutic option for 50% of hypertension patients (3). Within a few weeks of taking the treatment, these drugs can generate oral adverse oral (2,4). A history and a clinical examination can commonly indicate oral mucosal lesions. However, given the clinical resemblance of the lesions, they could occasionally go unnoticed (5). Specific patient- and drug-related variables are associated with the severity of the problems (6). Gender, age, underlying conditions, and genetics are all patient-related variables. Drug

delivery technique, duration, dose, and drug metabolism are among the aspects affecting medications (4). X erostomia, lichenoid responses, mucosal burning, dysgeusia, gingival hypertrophy, angioedema, and bleeding are among the undesirable side effects of anti-hypertensive medicines. (4). Although the pathophysiology of oral lichenoid reactions is still unclear, they can be induced by various systemic medications and metal fillings. Moreover, they are clinically and histologically comparable to lichen planus lesions although they are unilateral and have a traumatic pattern (7,8).

The lichenoid reaction caused by drug use was first reported in 1929. Later, it was documented by Almeyda and Levantine in scientific sources in 1971(9). These lesions appear as erythematous ulcers and, like oral lichen planus, are accompanied by Wickham Steriae, a group of whitish lines (10). The most crucial symptom of an accurate diagnosis is the recovery of these lesions a few weeks after quitting the medication. It can take weeks to months for lichenoid lesions to appear after taking a medication, with an average of 2 to 3 months (11). According to studies, lichenoid lesions brought on by drug consumption are becoming more common every day (12). The vast range of medications on the market and the higher drug intake among patients than in the past can be used to explain this escalating lichenoid lesion. This lesion is caused by various pharmaceuticals, the most common of them are nonsteroidal anti-inflammatory drugs and angiotensin-converting enzyme inhibitors (13,14). Other medications causing this injury are antimalarial medications (15,16) and antihypertensive medications (17,18). Drug use synergistically affects the incidence of lesions. One of the most apparent instances is Grinspan syndrome, which happens when antidiabetic and antihypertensive medications are used at the same time (19).

Every year, new antihypertensive medications are introduced to the market due to the various therapeutic approaches. Each has an amazing mode of action and, therefore, a unique set of adverse effects (20,21). Considering the rise in the number of patients with medication-related oral lichenoid lesions, and the scarcity of studies on new drugs and lack of study reports with precise statistics, this study aims to assess the prevalence of oral lichenoid reactions in patients taking antihypertensive medications.

Materials and Methods

Sample and Sampling Method

This descriptive, cross-sectional study was conducted in Urmia in 2021. Patients were selected from patients taking antihypertensive drugs who were referred to Seyed al-Shohada Hospital in Urmia until the sample size was completed and included in the study.

Patients taking antihypertensive medications made up the study's target population. Patients on beta-blockers, angiotensin-converting-enzyme (ACE) inhibitors, diuretics (particularly hydrochlorothiazide), captopril, methyldopa, furosemide, propranolol, spironolactone, labetalol, atenolol, enalapril, losartan, and combination drugs like Valsomix met the inclusion criteria (22-24). Exclusion criteria included use of drugs other than antihypertensive drugs, subjects with lichenoid reactions caused by contact with restorative materials, and refusal to participate.

The study by Kumar et al. (25) was used to estimate the sample size, with p=.4 and Z=1.95, obtained using the procedure below. To increase the likelihood of detecting samples with lesions caused by oral lichenoids, the sample size was increased from the original 366 antihypertensive drug users to 450 people.

The data collection instrument was a researcher-made questionnaire. It consists of demographic information and information related to the defects of oral liquid reactions, including the presence/absence of these defects, the location of the lesion, and presence of the lesion before using the medicine. It also elicited information about antihypertensive medications, including the type and the dose of medicine used, and how long the medicine has been taken. Content validity was utilized to verify the questionnaire's validity. Corrective opinions of 10 cardiologist and dentist professors were applied to develop the questionnaire. Reliability was calculated at .75 Cronbach's alpha.

Validity and reliability of the method

Patients were examined twice by two people (a qualified senior dentistry student and an oral disease specialist) separately in a double-blind manner. All the participants had received the necessary training in this field, and the type of waste was reviewed regularly. In the event of discrepancies between the observations, a third person performed the examination and evaluation of the lesion.

Data Collection

The data collection checklist consisted of three sections: patients' demographic information, information related to the lesions by oral lichenoid reactions, i.e., presence/absence of such lesions, the location of the lesion, and the existence of the lesion before using the medication, and information related to the antihypertensive medications like the type, the dose and the duration of medicine taken.

Research Procedure

A total of 450 patients on antihypertensive medications referred to Seyed al-Shohadai Hospital in Urmia-Iran were included in the study after receiving approval from the ethics committee of Urmia University of Medical Sciences and considering the inclusion and exclusion criteria. After receiving each patient's written consent, the study was carried out. The confidentiality of the examination data and the questionnaire was guaranteed to all patients. Following their stay at the hospital, the individuals' complete medical histories were obtained. If they were taking antihypertensive medicines at the time of the study, they were asked about the type of drug (brand name), drug dosage, duration of drug use, and other medications. A questionnaire was used to collect all the data, which was then matched with the patients' demographics (age, gender, etc.). The patients then underwent an intraoral exam by a senior dental student to determine if they had lichenoid reactions, which presented as a series of whitish lines (Wickham Steriae 6) (Figure1).

Figure 1. An Illustration of Lichenoid Reactions Diagnosed in the Studied Patients

A senior dental student and an expert in oral disorders independently performed two double-blind examinations on each patient. The type of lesions was periodically checked, and each participant had received the necessary training in this area.bbIf there was a discrepancy between the two observations, a third party examined and assessed the lesions. If the clinical diagnosis was unclear, a biopsy (in the mucosa and palate) was performed to confirm the clinical findings (10,26,27).

Data Analysis

The statistical software employed to analyze our data was SPSS™ version 26. To compare the variables, Chi-square and Spearman's correlation tests were utilized. *P-values* less than .05 were regarded as statistically significant.

Results

Approximately 281 (62.4%) of all patients in the study were female compared to 169 (37.6%) male patients. The mean maximum blood pressure was 121.1 ± 18.8, the mean minimum blood pressure was 77.5 ± 10, and the mean age was 58.6 ± 12.8 years. Furthermore, individuals took antihypertensive medications for an average of (0.2-480) 24 months. Table 1 lists the types and dosages of antihypertensive drugs.

Table 1. Type and Dosage of Antihypertensive Drugs in the Studied Patients

Type and dosage of antihypertensive drugs		Frequency	Percentage
Losartan		157	34.9
Dose	12.5	1	
	25	90	
	50	52	
	H50	14	
Valsartan		115	25.6
Dose	40	3	
	80	80	
	160	32	
Captopril		75	16.7
Dose	6.25	23	
	12.5	18	
	25	28	
	50	6	
Bisoprolol		104	23.1
Dose	1.25	2	
	2.5	81	
	5	20	
	10	1	
Nitroglycerin		145	32.2
Dose	0.4	9	
	2.6	94	
	6.4	42	
Furosemide		82	18.2
Dose	20	9	
	40	73	
Valzomix 8.5		9	2
Hydrochlorothiazide		61	13.6
Dose	12.5	22	
	25	25	
	50	14	
Carvedilol		62	13.8
Dose	3.125	21	
	6.25	37	
	12.5	3	
	25	1	
Amlodipine 5		39	8.7
Spironolactone		80	17.8
Dose	25	74	
	100	6	
Verapamil 40		1	0.2
Amiodarone 100		1	0.2
Metoprolol		25	5.5
Dose	25	5	
	47.5	13	
	50	6	
Propranolol		12	2.7
Dose	10	4	
	50	8	
Triamterene H25.50		1	0.2
Atenolol 5		1	0.2
Diltiazem 60		1	0.2
Enalapril		4	0.9
Dose	5	3	
	20	1	
Methyldopa 250		26	5.8

The results showed that losartan was the most widely used drug among the patients. Oral lichenoid reactions were observed in 15 (3.3%) of the 450 patients studied Chart 1. Prior to taking the medication, none of these individuals had mentioned having oral lichenoid lesions.

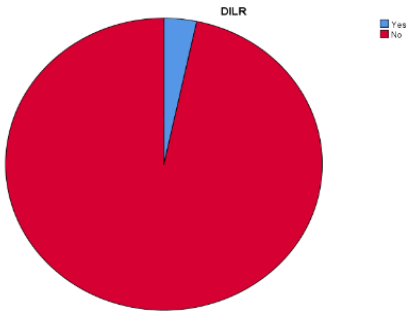

Chart 1. Prevalence of Oral Lichenoid Reactions in The Studied Patients

Patients who experienced oral lichenoid reactions ranged in age from 53.7 ± 7.1 years. Using Spearman's correlation test, it was determined that there was no significant link between age and developing oral lichenoid reactions (p=0.091). There were 10 (66.7%) women and 5 (33.3%) men among the patients who had oral lichenoid reactions. The results of the chi-square test showed a significant association between gender and oral lichenoid reactions (p=0.031), with women with hypertension developing oral lichenoid reactions more frequently than men with hypertension. Table 2 lists the antihypertensive medications taken by patients who experienced oral lichenoid reactions.

Table 2. Antihypertensive medications used in patients with oral lichenoid reactions

Antihypertensive drugs	Frequency	Percentage
valsartan	5	33.3
Hydrochlorothiazide	5	33.3
Methyldopa	5	33.3
Metoprolol	5	33.3
losartan	4	26.7
Propranolol	3	20
Bisoprolol	2	13.3

According to the chi-square test, there is no statistically significant difference between patients with oral lichenoid reactions and those who do not have oral lichenoid reactions when it comes to the frequency of use of valsartan, losartan and bisoprolol (p=.482, p=.497, and p= .361, respectively). However, patients with oral lichenoid responses used hydrochlorothiazide (p =.023), methyldopa (p =.000), metoprolol (p =.000), and propranolol (p =.000) more frequently than other patients.

The relationship between the dosages of each drug type in patients with oral lichenoid reactions was determined by the chi-square test, which revealed that in these patients taking valsartan 160 and metoprolol 47.5 was significantly more significant than other doses of valsartan and metoprolol (p=.000). There was no discernible difference between the doses used for other medications. In addition, patients who experienced oral lichenoid reactions took antihypertensive drugs for an average of 1 to 30 months. Moreover, the duration of antihypertensive drug use (3 months) was significantly shorter in patients with oral lichenoid reactions than in other patients, according to Pearson's correlation test between the two variables (450 patients).The average time spent on antihypertensive medications was 24 months (P=0.000). In 10 patients with oral lichenoid reactions, the buccal mucosa, labial mucosa, and retromolar region were the locations of the lesions.

Discussion

In the early stages of pathophysiology, hypertension is often asymptomatic and lacks a clear etiological cause. Because of this, many patients do not recognize it until the disease status worsens, making it difficult for the therapist to manage (28). As a result, many patients continue to use medication to manage their disease symptoms (29). Numerous studies rank antihypertensive medications among the most commonly prescribed. Some studies associate the use of antihypertensive medications with patients who develop oral lichenoid reactions (13,14,17,18). Nevertheless, numerous antihypertensive medications have been introduced, necessitating research into how they affect the frequency of oral lichenoid reactions (20,21). The aim of the current study was to assess the incidence of oral lichenoid reactions in patients receiving antihypertensive drugs. According to the findings, 3.3% of patients receiving antihypertensive drugs experienced oral lichenoid reactions. Before using the medications, none of these individuals had mentioned having oral lichenoid lesions. Similar to the present study, Kumar et al. reported that only 4.5% of patients utilizing antihypertensive patientshad lichenoid lesions (31). Additionally, 1% of the sample population in Qazvin city reported oral lichenoid lesions, according to a study by Burhan Mojabi et al (32).

No significant correlation was seen between age and oral lichenoid reactions in the current study with patients aged 53.7 ± 7.1 years. Until recently, it was assumed that people in their middle and fifties were the most likely to develop oral lichenoid lesions (33,34). One patient with drug-induced lichenoid lesions who participated in Kaomongkolgit's study was in his 50s (35). Most patients in Kumar et al. were 41 to 60 years old (31), and the patients in the study by Seyyed Majidi et al. were in their 50s (36).

In the current study, 66.7% of patients with oral lichenoid reactions were women, and 33.3% were men, indicating that the incidence of oral lichenoid reactions was higher in women than in men. In consensus with the present study, the incidence of oral lichenoid reactions was higher in women than in men in the studies by Kumar et al. (31), Seyyed Majidi et al. (36), and Dunsche et al. (37). Furthermore, in the current study, the buccal mucosa was the most common area affected by lesions in patients with oral lichenoid reactions. Moreover, the buccal mucosa was the most frequently lesion-involved site in Seyyed Majidi et al (36).

In this study, patients with oral lichenoid reactions took antihypertensive medicines for an average of three months. Patients who experienced oral lichenoid reactions required antihypertensive medication for a significantly shorter period of time than other patients. According to findings by Seyyed Majidi et al. which are consistent with our own in this regard, lesions can be formed in as short as one month and as long as 36 months (36). It appears that oral lichenoid reactions manifest not long after taking blood pressure medications

Valsartan, hydrochlorothiazide, methyldopa, and metoprolol were the most often used drug types in these patients, followed by losartan, propranolol, and bisoprolol, which was the least frequently used antihypertensive medication. The frequency of the use of hydrochlorothiazide (particularly 25mg), methyldopa (250mg), metoprolol (especially 47.5mg), and propranolol (especially 50m) was substantially more significant in patients with oral lichenoid reactions than in other patients. Although valsartan, losartan, and bisoprolol were not statistically different between patients with oral lichenoid reactions and other patients in terms of the frequency of use, the type of angiotensin receptor antagonists includes valsartan and losartan; the class of beta-blockers includes bisoprolol, metoprolol, and propranolol; the class of di-alpha-blockers includes methyldopa; and the class of diuretics includes hydrochlorothiazide(30). The use of hypertension medications (beta-blockers, angiotensin receptor antagonists, and diuretics) was found to be the most frequent cause of lichenoid lesions induced by drug use in a review study by Yuan et al.(38). Antihypertensive beta-blocker drugs were reported by Seyyed Majidi et al. as the most common class of drugs causing lichenoid lesions (36). As additional medications related to oral lichenoid reactions, Jayakaran's review study also listed hypertension medications, angiotensin-converting enzyme inhibitor medications, and beta-blocker medications like propranolol (39). According to a review study by Yousefi et al. hypertension drugs such as metoprolol and hydrochlorothiazide were the main etiological factors for dry mouth. Dry mouth is the most common cause of oral lichenoid reactions after taking drugs (5). According to Fortuna et al., the most typical medicine producing oral lichenoid

reactions brought on by drug use was methyldopa (40).

Limitations of the study

The present study has some limitations. Firstly, it was a single-center study, therefore, it isn'teasy to generalize the findings of this study to the whole population. Another limitation of the study was that patients taking other medications along with blood pressure medications and patients with lichenoid reactions due to contact with restorative materials were excluded from the study. For future studies, it is proposed to study these patients to examine the effect of these medications on the formation of oral lichenoid reactions.

Conclusion

Overall, oral lichenoid reactions occurred in 3.3% of antihypertensive medication users. Valsartan, hydrochlorothiazide, methyldopa, and metoprolol were the most often prescribed drug groups for these patients. Losartan, propranolol, and bisoprolol came in second, third, and fourth, respectively. Patients who experienced oral lichenoid reactions had considerably higher rates of hydrochlorothiazide (particularly 25mg), methyldopa (250mg), metoprolol (especially 47.5mg), and propranolol (especially 50mg) than other patients.

Conflicts of Interest

The authors have no conflict of interest to report.

Acknowledgments

This research was a cross-sectional study approved by the ethics committee of Urmia University of Medical Sciences with the ethics code IR.UMSU.REC.1400.108. We thank all the patients who participated in this study and permitted us to analyze their data to reduce the Oral lichenoid reactions.

Authors'Contributions

All authors contributed to collecting data and writing the manuscript. All authors have read and approved the manuscript.

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