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Literature Review

Oral Pathology Secondary to the Use of Antihypertensive Drugs Encountered in Odontological Patients: A Comprehensive Literature Review

Vilela CR[1], Ferreira KF[1], Magalhães MSC[1], Fonseca DP[2] and Heleno JFG[3]*

[1]*School of Dentistry, University Center Newton Paiva, Belo Horizonte, Brazil*

[2]*School of Biological Sciences and Health, University Center Newton Paiva, Belo Horizonte, Brazil*

[3]*Core Institute of Teaching and Research Hospital of Baleia Benjamin Guimarães Foundation, Belo Horizonte, Brazil*

***Corresponding Author**: Heleno JFG, Core Institute of Teaching and Research Hospital of Baleia Benjamin Guimarães Foundation, Belo Horizonte, Brazil.

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Abstract

Background: Systemic arterial hypertension is currently a disease of high prevalence thus patients with antihypertensive treatment are frequently encountered by periodontists. The relationship between antihypertensive drugs and the oral changes observed their use is reviewed.

Methods: Data collection was conducted through an extensive literature review of bibliographic research published in the last 15 years using Google Academic, LILACS, MEDLINE/PubMed and similar databases.

Results: The reviewed literature showed oral alterations related to the used of antihypertensive drugs is commonly encountered by oral surgeons. The most frequent were: xerostomia, hyposalivation, drug induced gingival hyperplasia, angioedema, alterations in the palate, aphthous stomatitis, pemphigus and lichenoid eruptions.

Conclusion and Practical Implications: This review alerts dental surgeons on the expected oral pathological complications encountered in patients under antihypertensive management.

Keywords: *Oral Lesions; Antihypertensives; Adverse Effects; Oral Manifestations; Systemic Arterial Hypertension*

Introduction

The number of patients with hypertension is increasing thus, individuals with cardiovascular diseases, cerebral accidents and renal diseases are on the rised which represent a global health challenge [8]. Currently health professionals are receiving patients with oral manifestations secondary to the use of several types of pharmacos. This trend suggests that in the future health professionals, including oral surgeons, could encounter an even larger number of patients with hypertension suffering from adverse drug related reactions.

Hypertension is a chronic non-communicable disease of high prevalence in the world. It is considered an extremely common cardiovascular disorder in the elderly, but it may be present in any age group [33]. It is estimated that 26.4% of the world's adult population, approximately 972 million people, have had hypertension in 2000 and half are unaware. In 2010 this number increased to 31.1%, data having a great impact in public health [8]. Thus, it is important to evaluate a patient in an integrated manner, through a well-conducted anamnesis, a good physical examination and the joint work of health professionals, doctors and oral surgeons, so that a correct diagnosis and an appropriate therapy may be implemented [34].

Several studies reported antihypertensive drugs can cause secondary adverse effects in the oral cavity, thus most of these cases have been linked to patients under dental care [23]. Therefore, dental surgeons should be familiar with drugs used in other conditions capable

of causing oral changes, particularly antihypertensive drugs. Although the pathogenesis of some of these events is still unknown, the observed pathological changes could be related to allergic reactions triggered by the systemic administration of these drugs, which could lead to exacerbate inflammatory reactions, such as drug induced gingival hyperplasia.

The data collection of the present review was done through indirect documentation, with an extensive bibliographical research in scientific articles available the Google Academic, LILACS, MEDLINE/PubMed and other databases. The search was carried out using keywords related to the topic, such as: hypertension, antihypertensive, oral changes, pathophysiology. To restrict the search to the subject of interest the selected words were used alone and/or in combinations. Using the appropriate keywords the study searched the data base of the last 15 years (2003 - 2018). The review included clinical trials and observational studies.

The collected data deals with the secondary side effects encountered by oral surgeons due to the administration of antihypertensive drugs. The review could be an aid to dental surgeons dealing with similar cases, which can be used to identify the correct approach to management and thus, alerting other health care professionals on the appropriate clinical care.

General aspects of systemic arterial hypertension

Cardiovascular disease is the leading cause of death worldwide. It affects 31.1% of the world's adults, approximately 1.39 billion people [8]. Resent global data on systemic arterial hypertension (SAH) showed a decrease in the mortality rate since the 1970s which has been linked to the available drugs to treat this disease [21].

Methodology

The data collection was done through indirect documentation, with an extensive scientific bibliographical review in the area of interest. The data was collected from national and international journals: LILACS, MEDLINE/PubMed and other databases using keywords topics such as: hypertension, antihypertensive, oral changes, pathophysiology. The keywords were used alone or in various combinations, to restrict the search to the subject of interest.

To refine the results, two criteria were considered: the time span and the language. Articles published in the last 15 years (2003 - 2018), in the Portuguese and English languages, were considered. These included reviews, clinical trials and observational studies. The data collection period took place between March and July 2018.

All selected bibliographies were analyzed and cataloged. This allowed the identification of the analyses by content, annotations of citations, presentation of the main ideas of the authors and location of the information relevant to the main subject.

Review of Literature

Systemic arterial hypertension

Cardiovascular diseases are the leading cause of death worldwide. Around 31.1% of the world's adults, approximately 1.39 billion people are affected [8]. Although global data showed systemic arterial hypertension (SAH) has a decrease in the mortality rate since the 1970s [21], his could be the result of the different drugs used for its management.

Systemic arterial hypertension is considered a chronic, non-transmissible disease characterized by sustained elevation of blood pressure levels equal to or above 140/90 mmHg (American Heart Association). Usually it occurs quietly but when the clinical manifestations are detected it is already at advanced stages of the disease, with a risk of irreversible damage to the patients´ health [30]. Although normal blood pressure limits are arbitrary, blood pressure levels equal to or below 120/80 mm Hg are considered ideal. Generally, above these values patient are at risk to develop cardiovascular diseases [17]. Hypertensive patients, even under control face pre-disposition to cerebral vascular accidents which is a public health problem that cannot be neglected [26].

The prevention of hypertension should include new strategies and updated approaches which may facilitate the identification of individuals at risk. At the time of diagnosis, treatment included non-drug strategies and the use of antihypertensive drugs, to reduce blood pressure and prevent disease progression [29].

Medicinal therapy for the treatment of hypertension

Diuretics

Diuretics are one of the first oral medications used to control blood pressure. They are prescribe in low dosage, easy to handle and low cost, which greatly facilitates therapeutic adherence [2].

By definition they are medications that increase the urinary flow and, consequently, the excretion of sodium and chlorine. As a result, there is a decrease in intravascular fluid and a reduction in pressure levels [12]. Diuretics are more frequently used as preventive drugs against stroke than antihypertensive drugs. They also act as Synergistics with other antihypertensives, potentializing their action [2,4]. These drugs differ in structure and in site of action within the nephron. Based on this differentiation three main classes are known: thiazide, loop, potassium-sparing [2].

Thiazides are diuretics acting through the luminal initial segment of the distal convoluted tubule blocking the sodium and chlorine cotransporter. At this site, sodium reabsorption usually occurs during kidney filtration (5 to 8%). As a result, a reduction in the volume of plasma and extracellular fluid could lead to a decrease in cardiac output, and thus a decrease in blood pressure [2,4].

Although widely used and among the first-line drugs to initiate antihypertensive treatment, thiazide diuretics have undesirable or even intolerable adverse side effects, and thus substituted by other drugs types. Hypokalemia, hyponatremia, hyperuricemia, changes in calcium metabolism, glucose intolerance and insulin resistance. In addition, undesirable side effects on lipids, and erectile dysfunction among others can be observed in patients using thiazide diuretics.

Despite the side effects, it is important to remember that the adverse effects decreasing cardiovascular and cerebrovascular protective capacity of thiazide diuretics are dose dependent, and the adverse reactions are generally present at higher doses, which is not consistent with the usual doses of 12.5 mg to 25 mg per day. This greatly reduces the adverse side effects of the thiazide drug, making it a first-line drug in the treatment of high blood pressure [2,4]. The main thiazide diuretics are: Hydrochlorothiazide, Chlorthalidone and indapamide [2].

The loop diuretics act on the luminal membrane of the thick ascending limb of the loop of Henle (at this site 35 to 45% of sodium reabsorption occurs), blocking the reabsorption of sodium chloride by inhibiting the sodium, potassium and chlorine co-transport system. Thus, loop diuretics are more potent and their onset of action is much faster. However, these drugs are not as effective at lowering blood pressure because they short acting action. It is has been reported that in the remaining hours sodium retention occurs, so the liquid balance of fluids during 24 hours remains unchanged. Due to their shorter action time, loop diuretics have fewer adverse side effects [2,4]. The main loop diuretics are: furosemide, torsemide, etacrynic acid and bumetanide [2].

Potassium sparing diuretics act on the luminal epithelial membrane of the distal convoluted tubule and collector, blocking the sodium channels this in turn leads to sodium channel hyperpolarization on the luminal membrane. Thus, this action reduces negativity in the lumen membrane and transepithelial voltage, which leads to reduced potassium execration [12]. They are widely used in clinical practice in patients with increased potassium excretion. The main potassium-sparing diuretics are: amiloride and triamterene [2].

Calcium channel blockers

Calcium channel blockers are divided into two basic types: dihydropyridine and nondihydropyridine. Dihydropyridine is predominantly vasodilatory drug and exerts little influence on heart rate and systolic function. A quality often used as antihypertensive management drugs. This group includes: amlodipine, nifedipine, felodipine, nitrendipine, manidipine, lercanidipine, levamlodipine, lacidipine, isradipine, nisoldipine, nimodipine [3,28]. The non-dihydropyridine has a lower vasodilatory effect and a greater action in bradycardia and antiarrhythmic making its use restricted to few specific cases. This group includes verapamil and diltiazem [3].

These drugs act as blood pressure reducers by decreasing the calcium concentration within cardiac and vascular smooth muscle cells rather than by inhibiting the transmembrane influx of the calcium ion (as the diuretics) case of, primarily by reducing peripheral vascular resistance [3,4].

In patients with hypertension, a single daily dose provides clinically significant reductions in blood pressure over the following 24-hour. Due to its slow onset of action, acute hypotension is not a characteristic of the administration of these medications. The most used drugs of this class are: amlodipine, diltiazem, nifedipine and verapamil [2,4].

Direct vasodilators

These drugs mode of action is vasodilation through nitrates entering the smooth muscle cells and acting at the opening of the ATP-dependent potassium channels. As a consequence, relaxation of the smooth muscle and reduction of peripheral vascular resistance occurs [2,4].

Hydralazine is one of the drugs that represents this class and is commonly used with a beta-blocker and a diuretic [2,3]. Some adverse reactions of hydralazine are headache, flushing, tachycardia, anorexia, nausea, vomiting and diarrhea. It may also cause lupus-like syndrome [2,3].

Another representative in this group is minoxidil. This drug acts by the opening of the ATP-dependent potassium channels, leading to relaxation of the smooth muscle. It is commonly used together with a diuretic and an adrenergic inhibitor to regulate hypertension [2,3].

Angiotensin converting enzyme inhibitors - ACEIs

IECAs are highly effective antihypertensive drugs in the treatment of hypertension and in the management of heart failure. They have a great impact on the reduction of cardiovascular morbimortality, thus widely used [2-4].

Its main action is the inhibition of the angiotensin converting enzyme (ACE) enzyme, thus preventing the transformation of angiotensin I into angiotensin II (substance that has vasoconstricting action). In addition, the reduction of angiotensin II leads to decreased secretion of aldosterone. As a result, increased renal sodium excretion occurs [2,4]. The main ACEIs are: captopril, enalapril, lisinopril, ramipril, perindopril and trandolapril [2,20].

Angiotensin II receptor blockers -BRAs

BRAs antagonize the action of angiotensin II by blocking its specific "AT 1" receptor. Activation of this receptor by angiotensin II is responsible for the actions of vasoconstriction, sympathetic activation, cellular proliferation, renal sodium reabsorption and release of aldosterone. Therefore, in the treatment of Arterial Hypertension, especially in patients at high cardiovascular risk or who have comorbidities, a reduction of cardiovascular and renal morbimortality is observed. For example, patients with diabetic nephropathy BRAs therapy displayed numerous clinical benefit [2,3].

Representatives of the BRAs class are: losartan, candesartan, eprosartan, irbesartan, olmesartan, telmisartan and valsartan [2].

Direct renin inhibitors

According to [25] aliskiren is the most modern drug and the punic representative of this class to be approved for the treatment of hypertension.

Aliskiren bind to the renin that is stored inside the cells, blocking its catalytic site. As a consequence, there is a decrease in the formation of angiotensin I and its conversion to angiotensin II, which results in a drop-in blood pressure [2].

This class of antihypertensive reduces blood pressure and, apparently, when combined with an ARB, there is an additional antihypertensive effect and protection of the target organ [2].

Alpha-1 adrenergic antagonists

These drugs classes act as competitive antagonists of post-synaptic alpha-1 adrenergic receptors. As a consequence, the activation of these receptors by circulating catecholamines does not occur, which leads to a decrease in peripheral vascular resistance without major changes in cardiac output. In addition, indirectly, these drugs enhance the activation of pre-synaptic alpha-2 receptors by circulating catecholamines, thus reducing neurotransmitter release through a negative feedback mechanism [2].

The antihypertensive effect of this group is discrete when used as monotherapy and is preferably used in combination with other antihypertensive drugs [3]. Recently, the drugs in the group started to be used, almost exclusively for the treatment of benign prostatic hyperplasia [2].

Some of the antihypertensive drugs in this class are: doxazosin, prazosin, terazosin, phenoxybenzamine, clonidine, guanfacine and methyldopa [3,4].

Beta-adrenergic antagonists

Beta-blockers or beta-adrenergic antagonists have for many years been used as anti-hypertensive drugs of second choice, soon after the diuretics, which are the first-line of therapeutic drugs. However, over time, it was observed that they could not reduce the incidence of heart attacks more effectively than the other classes of antihypertensives and thus offered less protection against strokes [2].

The mechanism of action of beta-blockers in arterial hypertension is still not well understood. In general, they act competitively by blocking beta receptors, selectively (beta 1 only) or nonselective (beta 1 and beta 2 receptors). One of the disadvantages of non-selective beta-blockers is the fact that they block the beta 2 receptor in the bronchial smooth muscle, which makes them contraindicated in some cases [12].

The main drugs of this class are: acebutolol, atenolol, betaxolol, bisoprolol, carteolol, carvedilol, esmolol, labetalol, metroprolol, nadolol, nebivolol, penbutolol, pindolol, propranolol, timolol [2].

Common oral changes observed during the use of anti-hypertensives drugs

Xerostomia

Xerostomia is an oral disorder characterized by the sensation of dry mouth. It occurs as a consequence of the decrease in the amount of saliva in the oral cavity. This may increase the predisposition to the appearance of carious lesions, inflammation of the mucosa and fissures in the dorsal part of the tongue [1]. To obtain the appropriate diagnosis some characteristics should be taken into account: burning in the mouth, difficulty swallowing, appearance of lesions due to prostheses maladaptation, dysgeusia, and difficulty to chew, among others [11].

There is no effective treatment for xerostomia. The use of sugar-free bullets to stimulate salivary flow and the use of oral hygiene products are behaviors adopted to attenuate the symptoms [1]. The use of artificial saliva applied according to the patient's disability, and water intake more frequently are alternatives treatments [11].

This change is common in elderly patients due to medications. To alleviate this drawback, decreasing, suspending or changing medication, are some of the alternatives [1].

The antihypertensives involved in xerostomia are: methyldopa, chlorothiazide, furosemide, metoprolol and calcium channel blockers [1].

Hyposalivation

Hyposalivation is characterized by decreased salivary flow, which may be associated with the use of certain drugs, especially antihypertensive drugs [18]. As oral alterations may occur, pain, gingivitis, halitosis, caries, ulcerations due to the use of prosthesis without retention and even candidiasis can be induced due to lack of salivation [7].

A sialometry test is necessary. This exam measures the amount of saliva secreted by the patient [7].

According to [18] the relationship between the mechanism of action of antihypertensives and the salivary glands has not been yet verified. It is believed that ischemia could cause a decrease in blood distribution to the salivary glands and buccal mucosa resulting in loss of salivary flow.

The use of artificial saliva is indicated, as well as the consumption of fresh drinks, citrus fruits, ice and chewing gums [7].

The antihypertensives causing hyposalivation are: captopril, enalapril, lisinopril, metroprolol, propranolol, atenolol, methyldopa, guanfacine, clonidine and others [7].

Angioedema

It is characterized by soft tissue elevation as a consequence of diffuse edematous volume that can affect even the connective tissue. It could be related to allergic reactions, mediated by immunoglobulin E (IgE) or drug-induced [1].

The use of angiotensin-converting enzyme (ACE) inhibitor drugs may lead to angioedema. It is mainly manifested by lip, tongue or face edema [10]. According to [10] the manifestation of Angioedema by this group of drugs is related to the high levels of bradykinin (vasodilator), since the ACE inhibits its degradation [1]. The management of allergic angioedema incudes the use of oral antihistamines is indicated. For drug-induced angioedema it is recommended that the patient be observed for some periods of time [1]. The ACEI drugs causing angioedema are: captopril, enalapril and lisinopril [6].

Gingival hyperplasia

Gingival hyperplasia is the abnormal growth of the gingival tissues. However, the term drug-induced hyperplasia is considered inappropriate, because the histological alterations lack the presence of hyperplastic or hypertrophic characteristics, neither in the epithelium nor in the cells of the connective tissue. The increase of periodontal tissue, in this case, is considered a non-neoplastic alteration and, when induced by any drug, is considered and inflammatory process and/or an immunological host response. According to [31], some drugs administered systemically are capable of modifying the inflammatory and immunological response of the gingival tissues.

Histologically, four characteristics are observed in the affected tissues: acanthosis, fibroplasia, excess collagen and secondary manifestations of inflammation. According to [1] the remodeling of gingival collagen is continuous and extremely controlled to maintain the

volume of gingival tissue constant, so the drug-induced gingival increase presents/displays more quantity/synthesis of the extracellular matrix, highlighting the collagen.

Clinically speaking this growth happens mainly in the region of the interdental papillae, but in extreme cases the dental covering can be also affected. The color of the gingiva may be more reddish or normal and depending on the degree of inflammation the texture of the mucosa may vary between flat, pointed or granular.

As discussed above, the calcium channel blocker Nifedipine is the most reported in longitudinal studies and presents a prevalence of gingival increase of 47.8%. Nifedipine induces accumulation of calcium and stimulates the metabolism of testosterone, affecting the events of collagen biosynthesis in fibroblasts, so the male sex is more susceptible to this alteration [19].

The antihypertensives causing gingival enlargement belong to the class of calcium channel blockers, being: Amlodipine, Bepridil, Diltiazem, Felodipine, Nicardipine, Nifedipine, Nimodipine, Nitrendipine and Verapamil [1].

Palate changes

The perception of the palate is obtained by the presence of buds or corpuscles gustatory. These small neurosensitive bodies are mostly located in the epithelium of the tongue and are also found in the larynx, soft palate, hard palate, vermilion of the lip, jugal and epiglottic mucosa and in the buccal floor. They are found with abundance in the oral cavity and according to [27] with the advancement of age these taste buds tend to diminish, undergoing a process of degeneration, which progressively diminishes the palate.

This alteration can be aggravated by the prescription of systemic drugs [13]. Amaral SM., *et al.* [6] pointed out that the way this drug-induced abnormality is not yet completely understood, but loss of taste (ageusia), diminution of taste sensitivity (hypogeusia) or distortion of correct perception of the substance may be present, for example, salty and sweet (dysgeusia). Taste changes caused by drug administration are extremely common and usually temporary. The antihypertensive drugs causing changes in the palate belongs to the class of ACE inhibitors, such as Enalapril [13].

Recurrent aphthous stomatitis

This is the most common pathological change found in the oral mucosa secondary to drugs management. Its appearance involves several factors classified as minor, major or herpetiform [1].

Minor ulceration presents a lower rate of recurrence. It appears predominantly in non-keratinized mucosa, with a removable white-yellow fibrinopurulent membrane and an erythematous halo around it that can measure between three and ten millimeters. It disappears without leaving a scar in a maximum of 14 days. Minor aphthous ulceration affects the labial and julian mucosa more, may also appear in the vestibule, soft palate, belly of the tongue and floor of the mouth [1].

Already the major ulceration lasts longer in the mucosa, measures one to three centimeters and can last for up to six weeks and may be recurrent. It can affect any area of the mucosa being more commonly observed in the labial mucosa, soft palate and amygdala [1].

In ulceration herpetiformis there are more lesions present and the rate of relapse is higher. Up to a hundred ulcers one to three millimeters in diameter may be observed. Healing occurs from seven to ten days and can affect any part of the mucosa [1].

According to [23] the etiology of stomatitis is unknown and may be multifactorial, local or systemic. Neville BW., *et al.* [1] suggest that as there are no causative agents, the destruction of the mucosa comes from an immune reaction caused by T cells, culminating in a decrease in CD4+ and TCD8+ T lymphocytes. Macrophages and mast cells increase in number causing necrosis.

Treatment is done according to the severity of the lesions. For mild aphthous ulcer there is no treatment but, if necessary, topical corticosteroid drugs may be used. In the case of increased ulceration, the use of stronger corticosteroids such as acetonide triamcinolone, which may be injected, is indicated, and other drugs may be applied as gel and ointments. Already the treatment for ulcerations herpetiform are also used corticosteroids making mouthwash and expectoration [1]. The use of the antihypertensive enalapril may lead to the onset of aphthous ulcers [6].

Lichenoid eruptions

Drug-induced lichenoid eruptions are bright, erythematous-violet polygonal papules that look like lichen on trees. Artico G., *et al*. [15] reported lichenoid reactions are less frequent in the oral mucosa than on the skin.

These eruptions closely resemble, clinically and histologically, with Flat Lichen, making their differential diagnosis difficult. According to [16] both sexes are equally affected, but lichenoid eruptions occur in 66 year-old adults, while lesions of lichen planus are more frequent in 50 year-old adults. Flat Lichen presents bright, flat, polygonal, violaceous papules and lichenoid eruption a more eczematous aspect, psoriasiform or pityriasis rosea. Histopathological examination reveals varying degrees of eosinophilic infiltrates and/or infiltrates of plasma cells in the papillary dermis [16].

According to [22] the classes of antihypertensives most commonly associated with the appearance of lichenoid eruptions are β-blockers, ACE inhibitors and diuretics (in particular hydrochlorothiazide). Neville BW., *et al.* [1] considered these eruptions caused by ACE inhibitors captopril and diuretics chlorothiazide, furosemide and spironolactone.

Drug-induced lupus-like

Drug-induced lupus-like clinical features caused by continued use of some drugs over a long period of time, providing patients with numerous forms of discomfort and symptoms [5].

Skin lesions are characterized by erythematous papules and also symptoms such as arthralgia. Other features that may be present are ulcerations, purpura, thrush and erythema nodosum. The mechanism of action is the inhibition of deoxyribonucleic acid (ADN) methylation, activation of monocytes (cells of the immune system) and metabolic disorders to certain drugs [5].

Systemic lupus erythematosus-like showed the presence of atrophic ulcerated areas containing white and thin streaks around. Other oral pathological changes such as marginal gingivitis and desquamative gingivitis may occur. The lesions are painful, thus oral hygiene is affected. This could contribute to the appearance of carious lesions and periodontal disease [1,14].

Histopathologically, the lesions present hyperkeratosis and thickening of the spinous layer. There is also epithelial atrophy, degeneration of the basement membrane and deep vasculitis [1,14].

According to [5] this disease affects more Caucasians and it is rare in people of African descendant. It is believed the incidence may be 15 to 20 thousand cases per year in the world of drug-induced lupus, with no difference in gender.

For the treatment of the disease it is necessary to identify the cause and then suspend the drug causing the change. In severe cases it is necessary the use of steroids [5].

Drugs inducing lupus-like symptoms are procaine and hydralazine. Lupus-like can be properly diagnosed after 12 months of induction. About 20% of patients taking procainamide, compared to 5% to 8% of those taking hydralazine.

Additionally, methyldopa has been related to this type of alteration [5].

Pemphigus-like eruptions (vesicular-bullous reactions)

A variety of chronic conditions can develop vesicular-bullous, ulcerative and/or erosive lesions in the oral cavity. According to [24] this condition can be a challenge for healthcare professionals in the clinical routine, as a differential diagnosis with vesicular-bullous lesions.

Another drug-induced oral manifestation cited in the literature is the vegetative pemphigus-like. This is a rare variant of pemphigus vulgaris that occurs in 1 to 2% of cases. This condition is different from the pemphigus vulgaris autoimmune disease that results in cutaneous blistering and sometimes involving the oral mucosa [9].

According to [1] the vesicular-bullous lesions may be due to the abnormal production of autoantibodies, which in turn recognize the surface glycoproteins of the epidemic cell as a foreign body, destroying them. These glycoproteins, desmoglein 1 and desmoglein 3, are components of the desmosomes (epithelial cell adhesion structures). The autoantibodies produced by the carrier of the disease obey these demmosomal components, breaking the molecular interaction responsible for the adhesion. This immune attack results in a cleft within the epithelium, causing the formation of an intraepithelial blister. These clefts may appear in varied areas, such as the parabasal layer (above the basal layer itself) of the buccal epithelium or epidermis.

Amaral SM., *et al.* [6] state that the pathogenic mechanism of vesicular-bullous reactions is not fully elucidated, however, the drugs may induce an immunological reaction that leads to the rupture of epithelial adhesion cells. The antihypertensive agents causing this change, according to [1,9] are the Captopril and Enalapril IECAs.

Discussion

The literature review revealed that many changes observed by oral surgeons are usually induced by the secondary side effects of antihypertensive drugs commonly used in patients with high blood pressure. Many of the antihypertensive drugs side effects reported by many dentists included oral mucosal lesions that need to be differentiated with clinical entities similar to that in other processes. For instances, Xerostomia and hyposalivation are two of these oral alterations. While hyposalivation causes a change in salivary flow, xerostomia represents a subjective experience of the patient, with the sensation of dry mouth. Although these changes are often confused, they are considered to be distinct changes and should be correctly diagnosed. For example, a patient with xerostomia should properly be differentiated from the symptoms found in patients with hyposalivation [7].

According to [1] the antihypertensives methyldopa, chlorothiazide, furosemide, metoprolol and the class of calcium channel blockers can cause xerostomia. On the other hand, due to similar clinical symptoms observed in cases of hyposalivation caused by captopril, enalapril, lisinopril, metroprolol, propranolol, atenolol, methyldopa, guanfacine and clonidine, their true etiology have been disputed. Thus, more studies are needed to understand the mechanism of action of these drugs [1].

The side effects of Angiotensin converting enzyme (ACE) inhibitors include hyposalivation and are also related to angioedema [1]. Amaral SM., *et al.* [6] confirmed that Captopril, enalapril and lisinopril representatives of this class, were involved in cases of hyposalivation as secondary side effects of these drugs. As was mentioned by [10] this clinical manifestation is related to the high levels of bradykinin, causing tissue deformation due to extravasation of plasma. Since the ACE inhibitors block the angiotensin converting enzyme, there is no degradation of bradykinin, causing vasodilation in conjunction with histamine, aggravating the condition. In addition, ACE inhibitors enalapril may cause changes in taste and aphthous ulcerations [13]. Recurrent aphthous stomatitis is the most common lesion affecting the buccal mucosa, but less frequently studied when it comes to drug-induced manifestations [1]. Despite studies on the subject, the pathophysiology of the secondary side effects of palate and recurrent aphthous stomatitis are not fully understood.

Regarding gingival hyperplasia, several groups of antihypertensive drugs secondary side effects are related to their appearance. However, it is important to note that calcium channel blocker, such as Nifedipine, has been the drug implicated in this oral disorder [1].

In addition [19] emphasize that the secondary side effects of this drug has a high prevalence on the appearance of gingival hyperplasia (47.8%). This drug acts by inducing calcium accumulation and stimulating testosterone metabolism, thus affecting the biosynthesis events of collagen in fibroblasts.

The induced Lichenoid Eruptions, which are clinically similar to Lichen Planus, are difficult to differentiate by most health professionals [15]. According to [22] it is common the appearance of lesions caused by the secondary side effects of antihypertensive classes of β-blockers, ACE inhibitors and diuretics (in particular hydrochlorothiazide). Neville BW., *et al.* [1] also reported similar observations and cited captopril, chlorothiazide, furosemide and spironolactone as secondary linkers to lichenoid eruptions.

Similarly, drug-induced lupus is a pathology rarely described in the literature. According to [5] it can be induced by the secondary side effects of procainamide, hydralazine and methyldopa, antihypertensive drugs, but they are seldomly used in the literature [5].

Finally, as reported by [6] the pathogenic mechanism of Pfigo-like eruptions (vesicle-bullous) has not been fully elucidated. However, it is believed that somehow the drugs induce an immune reaction that target the disruption of epithelial adhesion cells. According to [1,9] secondary side effects of Captopril and Enalapril are the drugs involved this pathology. Thus, it is perceived that ACEIs are often related to several oral disorders.

Conclusion

Oral surgeons play an important role in the care of patients suffering the secondary side effects of antihypertensive drugs used in conditions such as high blood pressure, a common global disease. It is up to the dental surgeon, not only to identify the oral lesions related to the use of this type of drugs, but also, to act in conjunction with other health care professionals, so the patients are properly assisted. In this context, the importance of a detailed anamnesis, thus that the dental surgeons could be aware of the patients´ prescribed drugs is of paramount importance. With this information and a thorough clinical examination, dentists could note unusual changes in the patient's oral cavity avoiding unnecessary therapies. The literature review revealed that, to understand the physiopathology of the disease symptoms, some of the above discussed conditions need further studies. Thus, more research is needed to investigate these conditions to select their proper management.

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