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Antihypertensive Medications Inducing Salivary Gland Dysfunction and Xerostomia: A Narrative Review

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Abstract: The aim of this study was to review the literature on the relationship between antihypertensive drugs and reduced salivary flow (hyposalivation) and the sensation of dry mouth (xerostomia). An exhaustive search of the literature was carried out, with no prior date limit until 31 August 2022, on PubMed, Google scholar and the Cochrane Library. The search terms were: saliva, xerostomia, hyposalivation OR salivary flow AND hypertension, antihypertensive drug, OR antihypertensive drugs. The overall prevalence of xerostomia in this population of hypertensive patients on pharmacological treatment was 21.1%. For the relationship between antihypertensive drugs and salivary secretion, the type of antihypertensive studied in the literature included β-adrenergic blockers, diuretics, α-adrenergic blockers, calcium channel blockers and cardiac glycosides. In some studies, the type of antihypertensive was not available. Many studies measured unstimulated salivary flow to assess hyposalivation. Three studies showed a non-significant increase in unstimulated salivary flow after treatment with β-adrenergic blockers or angiotensin converting enzyme (ACE) inhibitors. One study found a statistically significant decrease in unstimulated salivary flow in normotensives treated with propranolol and phentolamine, which are both non-selective β-blockers. Two studies showed no significant decrease in unstimulated salivary flow after treatment with diuretics. For stimulated salivary flow, one study had no significant changes in patients treated with captopril (ACE inhibitor) and two others had a significant decrease after treatment with furosemide and bendroflumethiazide (two diuretics). A single study shows that the percentage of patients with hyposalivation was significantly higher in hypertensive patients treated with ACE inhibitors, calcium channel blockers, β-adrenergic blockers, and diuretics. Future studies are needed and may help to understand which antihypertensive is most appropriate for patients to avoid reduced salivary flow and dry mouth.

Keywords: Arterial Hypertension, Antihypertensives, Salivary Gland, Dysfunction, Salivary Flow, Xerostomia, Hyposalivation

1. Introduction

Saliva plays a role in maintaining oral health by providing multiple defense functions, including homeostatic processes, lubrication, antimicrobial activity, and control of demineralization through remineralization of the teeth. Saliva also plays an essential role in the various orofacial functions (gustation, mastication, phonation, swallowing) [1, 2]. Saliva secretion is the result of complex processes subject to numerous nervous and hormonal regulations. The volume of saliva secreted per day is significant (around 0.75 to 1.5 liters per day). On average, the unstimulated flow is 0.3 ml/min, with an average total of 16 hours of unstimulated flow (rest and sleep periods). The maximum stimulated flow is 7 ml/min [3]. It is generally accepted that drug therapy is often associated with dry mouth (xerostomia), hyposalivation

(objective reduction in salivary flow) and changes in saliva composition [4]. More than a thousand drugs are thought to be associated with xerostomia and hyposalivation. Tricyclic antidepressants, muscarinic receptor antagonists, antipsychotics, opioids and benzodiazepines, antihypertensives and antihistamines are the main drugs producing this effect [5]. Antihypertensive drugs associated with salivary changes include β-adrenergic blockers, diuretics, angiotensin-converting enzyme (ACE) inhibitors and drug combinations [6]. These antihypertensives are a class of drugs that are administered to reduce high blood pressure. Arterial hypertension (AH) is a chronic disease characterised by an increase in systemic blood pressure. Blood pressure can be expressed in two measures: systolic blood pressure (SBP) and diastolic blood pressure (DBP), which are the maximum and minimum pressures. Table 1 compares previous thresholds [7] with current thresholds for hypertension [8, 9]. Hypertension is a major public health problem affecting more than a billion people worldwide. It disproportionately affects people in low- and middle-income countries, where health systems are generally weak. The rising prevalence of hypertension is associated with population growth, ageing, genetic factors and behavioral risk factors such as excessive salt and fat consumption, physical inactivity, overweight and obesity, harmful alcohol consumption and poor stress management. In the long term, hypertension carries a risk of cardiovascular events, such as heart disease, stroke, kidney failure, disability and premature mortality [10]. Non-pharmacological treatment with appropriate lifestyle modification is recommended for all patients with hypertension. In addition, antihypertensive drugs are recommended in many cases and should be considered in others who have not achieved a normal BP goal despite non-pharmacological treatment [11]. In terms of current guidelines for the management of hypertension, first-line antihypertensive drugs include ACE inhibitors, angiotensin II receptor blockers, beta-blockers, calcium channel blockers and diuretics [12]. However, central antihypertensives are used in certain circumstances. Although the side effects of antihypertensives have been extensively studied, their effects on saliva have not been clarified [6, 13].

Table 1. *Thresholds for hypertension screening.*

BP category	SBP (mmHg)	DBP (mmHg)
Previous guidelines [7]		
High	≥ 140 and	≥ 90
Current guidelines [8, 9]		
Normal	< 120 and	< 80
Elevated	120 to 129 and	< 80
Hypertension	Stage 1: 130 to 139 or	80 to 89
	Stage 2: ≥ 140 or	≥ 90
Hypertensive crisis	> 180 and/or	> 120

BP: blood pressure. DBP: diastolic blood pressure. mmHg: millimetres mercury. SBP: systolic blood pressure.

The aims of this review of the literature were: (1) to investigate the relationship between hypertension and salivary secretion, (2) to determine the prevalence of xerostomia and hyposalivation in patients taking antihypertensive drugs, (3) to identify which antihypertensive drugs produce more xerostomia and/or hyposalivation and (4) to explain the mechanisms by which antihypertensive drugs can cause xerostomia and/or hyposalivation.

2. Search Strategy

An exhaustive literature search was carried out, with no prior date limit until 31 August 2022. Three international literature databases were used to conduct the search: U.S National Library of Medicine (PubMed/MEDLINE), Google scholar and Science direct. These databases were searched for studies using the following combination of terms: saliva, salivary flow OR xerostomia, hyposalivation AND hypertension, antihypertensive drug, OR antihypertensives. These terms were adjusted according to each database. An additional manual search of the reference list of articles reviewed was performed to identify additional studies that could potentially be included in this review.

The results of this search enabled us to organize this narrative review into 3 themes:

1) hypertension and salivary secretion
2) Epidemiological data on hyposalivation and xerostomia in patients taking antihypertensive drugs,
3) antihypertensive drugs and salivary secretion

3. Hypertension and Salivary Secretion

There is little information on salivary gland function in hypertensive patients prior to antihypertensive medications. Ben-Aryeh *et al.* reported higher unstimulated salivary flow rates in normotensive patients than in hypertensive patients prior to treatment with the β-adrenergic blocker pindolol [14]. Rahn *et al.* in a similar study, also found higher unstimulated salivary flow rates in normotensive subjects than in mildly hypertensive subjects prior to treatment with propranolol [15]. Conversely, Niedermeier *et al*. in an earlier study, found no difference in unstimulated and stimulated salivary flow rates in hypertensive subjects compared with a normotensive control group [16]. Streckfus *et al.* found no difference in stimulated salivary flow rates from the parotid gland in normotensive and moderately hypertensive blacks [17].

It is difficult to compare the results of these four studies. Each investigator used a different method to collect saliva and determine salivary flow rates.

Furthermore, there is no clear physiological reason to believe that hypertension per se can influence saliva secretion.

More recent study has investigated the relationship between xerostomia, hyposalivation and antihypertensive drugs [13, 18-23].

4. Prevalence of Xerostomia and Hyposalivation in Patients on Antihypertensive Drugs

The overall prevalence of xerostomia in this population of

hypertensive patients on pharmacological treatment was 21.1% [21]. The prevalence of xerostomia in this study was very similar to that reported by Österberg *et al.* (21%) [24] and Locker (22.5%) [25] in people aged over 60. Xerostomia in healthy people was the lowest, compared with that obtained in patients on hypertensive medication [26]. Diabetic patients with hypertension had the highest prevalence of xerostomia compared with healthy patients [21]. The proportion of patients suffering from hyposalivation was higher in people complaining of xerostomia than in subjects not complaining of xerostomia [21].

In the study by Nonzee *et al.* which included 400 subjects, 200 of whom were ambulatory hypertensive patients taking antihypertensive medication and 200 control subjects, the prevalence rate of xerostomia in the hypertensive group taking antihypertensive medication was 50%, whereas only 25.5% of the control group had xerostomia, with a significant difference between the two groups ($p < 0.05$) [22].

Studies on the prevalence of hyposalivation and/or xerostomia in patients taking antihypertensive drugs are not abundant, and the existing studies are not of high methodological quality [17, 19, 21, 22, 26-29]. In some studies, the prevalence of hyposalivation was not available [17, 19, 21]. In addition, the clinical trials available on this subject are not up to date [14, 23]. The design of the studies was heterogeneous. At present, the available data do not allow us to define an exact prevalence of hyposalivation in hypertensive patients receiving pharmacological treatment.

5. Antihypertensive Drugs and Salivary Secretion

The type of antihypertensive studied in the literature included β-adrenergic blockers [14, 20, 22, 23, 29], diuretics [13, 17, 22, 27, 30, 31], α-adrenergic blockers [20, 29], calcium channel blockers [20, 22] and cardiac glycosides [20]. In some studies, the type of antihypertensive was not available [19, 21, 28].

Many studies measured unstimulated salivary flow to assess hyposalivation. Three studies showed a non-significant increase in unstimulated salivary flow after treatment with β-adrenergic blockers [14, 23] or angiotensin converting enzyme (ACE) inhibitors [26]. One study found a statistically significant decrease in unstimulated salivary flow in normotensives treated with propranolol and phentolamine, which are both non-selective β-blockers [29]. Two studies showed no significant decrease in unstimulated salivary flow after treatment with diuretics [27, 30].

For stimulated salivary flow, the results were also heterogeneous, showing that one study had no significant changes in patients treated with captopril (ACE inhibitor) [26] and two others had a significant decrease after treatment with furosemide and bendroflumethiazide (two diuretics) [27, 30].

The study by Nonzee *et al*. was the only one to show that the percentage of patients with hyposalivation was significantly higher in hypertensive patients treated with ACE inhibitors, calcium channel blockers, β-adrenergic blockers, and diuretics [22]. They showed that mean unstimulated salivary flow in the treated hypertensive group (23.11±6.08 mm/3min) was significantly lower than in the control group (31.30±3.36 mm/3min) ($p<0.05$). In addition, the mean stimulated salivary flow rate of the treated hypertensive group (0.73±0.30 ml/min) was also significantly lower than that of the control group (1.31±0.34 ml/min) ($p<0.05$). The factor most strongly associated with dry mouth and hyposalivation was the use of antihypertensive drugs (OR = 6.28) [22].

Among the antihypertensive drugs incriminated, two have been the subject of more studies: diuretics and beta-adrenergic receptor antagonists.

5.1. Diuretics and Salivary Secretion

Diuretics are one of the most prescribed drugs for the control of hypertension. The diuretic effect results in an overall decrease in intravascular and extracellular fluid volume, which in turn reduces cardiac output [32, 33]. Hydrochlorothiazide (HCTZ) and furosemide are two diuretics used to decrease cardiovascular volume; both are suspected of altering salivary secretion. The first study of diuretics and altered salivary function was conducted by Osterberg *et al.* [22]. These authors found a significant reduction in total saliva secretion stimulated using diuretics [22]. This study did not evaluate a particular diuretic, but a group of patients using several types of diuretic.

Because diuretic drugs are grouped together in a single category, it is not possible to distinguish the pharmacodynamic effect of each diuretic on salivary flow. Nederfors *et al*. (1989), studied the effects of a specific diuretic, bendroflumethiazide, which is a thiazide diuretic, on unstimulated and stimulated total salivary flow. Bendroflumethiazide promotes the excretion of Na+ and water by inhibiting their reabsorption in the distal renal tubule of the kidney [31]. In this double-blind, placebo-controlled crossover study, the authors found that treatment with low-dose bendroflumethiazide significantly reduced total stimulated salivary flow and total sodium production in 34 healthy volunteers [31]. The study also showed no change in unstimulated total saliva flow [31].

In a study assessing parotid function, Streckfus *et al*. investigated the effects of HCTZ on stimulated salivary flow rates from the parotid gland [17]. The study included three groups of subjects: normotensive subjects, hypertensive patients taking no medication and hypertensive patients whose blood pressure was controlled by HCTZ. The results of the study showed no difference in stimulated salivary flow rates from the parotid gland between the normotensive subjects and the subjects whose hypertension was not controlled, but there was a significant reduction in stimulated salivary flow rates from the parotid gland in the hypertensive subjects treated with HCTZ compared with the other two groups [17]. Atkinson *et al. (1*989), conducted a study on the effects of furosemide (a diuretic which acts on the Na+, K+, CL- cotransporter in the loop of Henle) on unstimulated

secretions from the parotid and submandibular/sublingual glands [34]. The study was a double-blind, placebo-controlled, crossover study involving five healthy, non-hypertensive subjects receiving a dose of 0.5 milligram/kilogram of furosemide. The results of the study showed no alterations in unstimulated salivary flow rates from the parotid and submandibular/sublingual glands, total protein levels or electrolyte compositions. However, subjects did experience a significant increase in the subjective sensation of oral dryness (xerostomia) [34]. Experimental treatment with furosemide resulted in a five-fold increase in urine output. However, analysis of salivary secretions showed that there were no significant differences in flow rates, total production, total protein or concentrations of Na+, K^+ or Cl^-, after administration of the drug or placebo. Subjectively, xerostomia was 10-fold more frequent after furosemide ingestion. These data suggest that in vivo, furosemide has a greater effect on the kidneys than on the salivary glands and that the sensation of dry mouth does not depend only on quantitative salivary secretion [34].

A more recent study by Nederfors *et al.* (2004) using furosemide or bendroflumethiazide, a diuretic as an antihypertensive, also analyzed the degree of xerostomia. They found that patients treated with bendroflumethiazide, or furosemide had higher levels of xerostomia [27].

In the study by Prasanthi *et al.* involving 100 patients divided between the test group and the control group according to the use of diuretics. A significant decrease in unstimulated saliva ($p<0.001$), stimulated saliva ($p<0.001$), salivary pH ($p<0.001$), and salivary concentrations of Na^+ ($p<0.001$) and Cl^- ($p<0.01$) ions were found in hypertensive patients on diuretics compared with the control group [13]. This study shows that diuretics significantly reduced salivary flow and altered salivary composition, which may have an impact on the incidence of dental caries, periodontal disease and the development of lesions in the oral mucosa [13].

5.2. Beta-Adrenergic Receptor Antagonists and Salivary Secretion

Studies have also examined the effects of beta-adrenergic blockers on salivary function. The oldest of these two studies was carried out by Ben-Aryeh *et al.* [14]. The population consisted of 10 normotensive subjects and 10 patients with hypertension who were to be treated with pindolol, a beta-adrenergic blocking agent. Total unstimulated saliva was collected from normotensive and hypertensive subjects before and after treatment with pindolol. Before treatment, the results showed that normotensive subjects had higher total unstimulated saliva flow rates than hypertensive patients [14]. After treatment of hypertensive patients with pindolol, their salivary flow increased and was statistically comparable to that of the normotensive control group [14]. In a similar study, Rahn *et al.* also found higher unstimulated salivary flow rates in normotensive subjects than in mildly hypertensive subjects. In addition, the study showed no further decrease in salivary flow when patients were treated with propranolol [15].

A clinical trial was conducted on 48 hypertensive patients treated with atenolol (beta-blocker) and 48 "normotensive" individuals (age- and sex-matched controls). Saliva was collected 2 to 3 times before atenolol treatment and 24 hours, 1 week and 4 weeks after atenolol treatment. The pH value was estimated. Salivary concentrations of sodium, potassium, calcium, magnesium, and total protein were measured. Salivary flow was estimated by measuring the volume of total saliva. The authors showed that hypertensive patients were characterised by lower salivary flow and significantly elevated levels of protein, potassium, and phosphate. They concluded that this could be linked to chronic adrenergic over-stimulation of the salivary glands in hypertensive patients. Salivary concentrations of sodium, calcium and magnesium were similar in both groups. Atenolol increased salivary flow and reduced phosphate but had no effect on protein and potassium concentrations [23].

5.3. Mechanisms of Action of Antihypertensive Drugs on Salivary Secretion

Although it is recognized in the literature that many antihypertensive drugs have the capacity to induce xerostomia and/or hyposalivation, the mechanisms by which these drugs act remain unknown for many of them. However, for some classes, explanations, or hypotheses of mechanism of action have been put forward.

Diuretics are antihypertensive drugs often used to manage hypertension and congestive heart failure. They increase natriuresis (evacuation of sodium in the urine) and lead to concomitant water loss. They lead to an overall reduction in intravascular and extravascular fluid volume. The increase in urine output during treatment with diuretics could be one of the reasons for the appearance of dry mouth in patients [35].

Calcium channel blockers are used for hypertension, arrhythmia, and stable angina pectoris. They block the slow calcium channels preventing calcium from entering the muscle cell, thereby limiting contraction. In the arteries, muscle relaxation leads to vasodilation. In myocardial cells, they inhibit the force of contraction. In a study conducted in Japan, Hattori *et al*. attempted to explain the mechanism by which calcium antagonists could cause xerostomia. They suggest that non-selective cations and calcium-dependent channels are involved in unstimulated salivation [36]. Calcium channel blockers, through their action on calcium-dependent channels, reduce water secretion from the salivary glands and this action may cause dry mouth [36]. Centrally acting antihypertensives act by decreasing sympathetic tone and increasing vagal tone through stimulation of central alpha-2 adrenergic receptors. This leads to a decrease in heart rate, vasodilation, and a reduction in the activity of the renin-angiotensin system. The secretory cells of the salivary glands are equipped with muscarinic adrenergic receptors, which are involved in the formation of initial saliva. It is understandable that drugs which have an antagonistic action on autonomic receptors can also affect the functions of the salivary glands and thus cause dry mouth [37]. A large data of the literature suggests that there are significant differences

in the effect of hypertension on saliva secretion [20, 27]. However, most of them indicate that patients with hypertension have a lower level of saliva secretion. The group of antihypertensive drugs includes several medications as: diuretics, cardiac glycosides, centrally acting antihypertensives, α-adrenergic blockers, β-adrenergic blockers, angiotensin converting enzyme (ACE) inhibitors, calcium channel blockers. They all have different mechanisms of action. Some act selectively, affecting the kidneys and heart, while others are called non-selective antihypertensives. The patients selected in several studies could not be grouped according to the type of drug they were taking to regulate their blood pressure, as most of them were taking a combination of two or more antihypertensive drugs. The decrease in salivary flow in patients with hypertension is directly related to the increase in diuresis in patients taking diuretics to treat their blood pressure. The increase in diuresis leads to a reduction in total extracellular fluid, which directly influences saliva production. However, drugs belonging to the calcium channel blocker group can also lead to a reduction in saliva secretion. In fact, inositol-3-phosphate, and calcium play an important role in regulating the secretion of water and electrolytes by the salivary glands [36, 37]. The concentration and ratio of electrolytes in saliva can vary significantly depending on the intensity of stimulation and the amount of saliva secreted.

Ivanovski *et al.* in their study, found differences in the mean values of Ca^{2+} in saliva between two groups (control and hypertensive). However, this difference was not statistically significant [20]. Increased salivary Na^{+} concentrations are the result of the use of diuretics, which inhibit Na^{+} reuptake in the collecting and draining ducts of the salivary glands, resulting in higher concentrations of this electrolyte being secreted. If we consider the fact that many diuretics do not spare potassium, but provoke its increased secretion, the result of increased salivary potassium concentrations found in the study by Ivanovski *et al.* is logical [20]. The author believes that the elevated potassium values are due to the action of the blockers on alpha receptors.

Urea is a carbonic acid diamide. The salivary glands do not synthesize urea, but it arrives by ultrafiltration from the blood serum. As the product of protein catabolism, urea acts as a moderately alkaline compound. It has a small molecular weight and passes easily through the membrane of acinar cells. The increase in salivary urea values in patients undergoing antihypertensive treatment may be the result of diet and increased protein intake in the diet of these patients [20].

The concentration of total protein in the saliva of patients on antihypertensive therapy is higher than in control subjects [20].

We suppose that the increased total salivary protein values are due to long-term adrenergic stimulation in hypertensive patients.

6. Clinical Implications

Some studies have shown a reduction in saliva secretion in hypertensive patients undergoing pharmacological treatment [20, 22, 29]. The significant reduction in the amount of saliva secreted and the alteration in the concentration of electrolytes in saliva in patients undergoing antihypertensive treatment are risk factors for numerous oral diseases and problems, such as the increased frequency of caries, periodontal disease, and bacterial and fungal infections. The reduction in salivary flow caused by antihypertensive drugs is a reversible process, as the parenchyma of the salivary glands is still preserved. Therefore, when dealing with patients on antihypertensive treatment, the dentiste should adopt the following guidelines:

1) Questioning of the patient: must investigate
   a) the circumstances of onset and manifestations of xerostomia,
   b) the psychological context (anxiety)
   c) eating habits (hard or soft foods, quality of chewing),
   d) medical problems and treatments associated with hypertension.
2) Examination of teeth (caries), oral mucosa (candidiasis, ulceration), extent of edentulism.
3) Measurement of stimulated and unstimulated salivary flow to determine the presence or absence of hyposalivation and measurement of the composition of salivary constituents (electrolytes and proteins).
4) The advice to be given in the event of hyposalivation or xerostomia is:
   a) humidify the oral cavity: water, salivary substitutes (e.g., bioXtra®, Pharmadent),
   b) stimulating salivary secretion: by chewing (for a long time, hard foods, sugar-free chewing gum, gustation (lemon juice), cholinergic agonists (e.g., pilocarpine, but only occasionally and in collaboration with the treating doctor to avoid chronic side effects and drug interactions), another sialogogue drug (Sulfarlem 25®).
5) Preventive treatment of caries and dental hypersensitivity hygiene, fluor therapy, dental monitoring, diet control.

7. Conclusion

Studies on the relationship between xerostomia and/or hyposalivation and antihypertensive drugs are rare. Only two clinical trials have shown a statistically significant decrease in flow after antihypertensive treatment, and one clinical trial has shown a statistically significant increase in flow after antihypertensive treatment. There is no evidence in the current literature that patients taking antihypertensive drugs suffer more from xerostomia or hyposalivation than patients not taking antihypertensive drugs. Furthermore, due to the great heterogeneity in the types of antihypertensive, the design of the studies and the different results, it was impossible to determine whether one antihypertensive produced more hyposalivation than another. Methodologically sound studies with adequate sample size to provide solid evidence should be conducted. Long-term randomized clinical trials are also needed to analyze the

effects of antihypertensive drugs on salivary secretion. It would be interesting to carry out long-term clinical trials in which different antihypertensive drugs at standardized doses are tested against placebo/CG to elucidate which drug reduces salivary flow more. This would enable doctors to choose the antihypertensive best suited to patients to limit hyposalivation and its impact on the oral cavity.

Conflict of Interest

Authors of this study have no conflict of interest.

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