

## Amlodipine and Xerostomia in Elderly Patients

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### Abstract

Hypertension is one of the most common chronic diseases worldwide. The prevalence of hypertension in the elderly is high and many of them are taking different types of antihypertensive medications including Amlodipine. Xerostomia and hyposalivation can have a detrimental effect on a patient's quality of life leading to situations such as stress or anxiety.

In this study, the relationship between Amlodipine as an antihypertensive drug and xerostomia in elderly patients was evaluated. 72 patients of both genders aged 65-75 taking amlodipine for the last 3 years were involved in the study. Those patients have shown xerostomia or hyposalivation in variable degrees. The percentage of xerostomia in the medicated hypertensive group of the present study was higher in males (22 %) than those in females (20 %) which was not significant ( $p = 0.705$ ). However, a statistically significant difference ( $p = 0.003$ ) between amlodipine and xerostomia status was observed which was higher in males (34.7 %) than that in females (26.4%).

This study assures that elderly patients taking Amlodipine are at high risk of having xerostomia and hyposalivation.

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### Introduction

Hypertension is a chronic medical condition in which blood pressure is elevated in the arteries. This medical condition is common, and the incident had increased substantially in the last 20 years. To control blood pressure, several classes of drugs are commonly employed, among them are angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers, beta-blockers, diuretics, and calcium-channel blockers<sup>1</sup>.

Many classes of anti-hypertensive medications have been reported to cause dry mouth-associated side effects. Most of these

classes are thought to cause dry mouth via activation of the central nervous system and alpha-2-adrenergic receptors in the salivary gland. Some newer classes of anti-hypertensive drugs, such as moxonidine and rilmenidine are claimed to modulate blood pressure without affecting salivary flow. In one study, where moxonidine was compared to other classes of anti-hypertensive, subjects receiving moxonidine only reported a marginal incidence of dry mouth, compared to a significantly larger population that complained of dry mouth in other anti-hypertensive classes<sup>2</sup>. Regardless, due to various reasons, conventional anti-hypertensive classes such as calcium channel blockers (CCBs) are still a popular choice in the current clinical setting to manage hypertension.

Amlodipine is a popular calcium channel blocker (CCB) in the clinical setting and is involved in various patient management strategies. It was initially prescribed for coronary heart disease and various medical conditions such as angina, peripheral vascular disease, and arrhythmic conditions. At the later stage,

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amlodipine is profoundly acknowledged for its efficacy in controlling blood pressure and has thus been prescribed to control hypertension, it has some advantages compared to the other agents in the class.

Amlodipine primarily inhibits calcium influx into myocardial and vascular smooth muscle cells, relaxing the blood vessel, and thus resulting in the decrease of peripheral vascular resistance. It is a third-generation CCB that has a long-acting effect attributed partly to lipophilic characteristics. It has higher bioavailability within its class, ranging from 60% to 80%. The slower elimination time of amlodipine, over 60 hours compared to the other CCBs also contributes to the high bioavailability of this drug<sup>3</sup>. As amlodipine has a long half-life, it can be given once daily, thus improving patient compliance. The recommended starting dose of amlodipine is 5 mg daily, with a maximum permissible dose of 10 mg daily. For populations with hepatic failure and the elderly population, a 2.5 mg starting dose is indicated.

Apart from that, amlodipine demonstrated lesser adverse effects associated with CCBs. Commonly, a patient receiving CCBs such as atenolol and metoprolol tends to complain of palpation and increased heart rate. First-generation CCBs are also commonly associated with increased Pulmonary vascular resistance (PVR) and dysregulation of lipid and carbohydrate metabolism. These notable adverse effects are reportedly lesser in patients taking amlodipine<sup>4</sup>.

Saliva is an essential body fluid with several functions essential for maintaining oral health. Xerostomia, also known as dry mouth in layman's terms, is referring to complaints of dryness on the lips and mouth cavity. On the other hand, hypo-salivation is a medical condition where salivary production is reduced. Unlike hypo-salivation, which is defined by reduced salivary flow, xerostomia is more subjective in nature<sup>5</sup>.

Xerostomia is reported in Sjögren's syndrome and systemic metabolic disorders like diabetes mellitus. It is also often commonly reported as a side effect of drugs and radiotherapy. Many medications are associated with xerostomia as a side effect, amongst them anti-hypertensives, opioids, tricyclic anti-depressants, muscarinic receptor antagonists, anti-psychotics, benzodiazepines, and

antihistamines<sup>6</sup>. Notably, several antihypertensive drugs such as  $\beta$ -adrenergic blockers, diuretics, ACE inhibitors, or a combination of the above have been reported to cause xerostomia<sup>7</sup>. However, little is known about the incidence of xerostomia in the elderly population taking amlodipine.

Saliva secretion is controlled by the endocrine system. One of the pivotal hormones in regulating saliva production is aldosterone. Aldosterone regulates the metabolism of sodium and potassium and indirectly participates in the regulation of the metabolism of chlorine in the salivary gland. Under the influence of aldosterone, sodium ions are reabsorbed from the salivary glands into the bloodstream, while potassium ion is secreted into saliva. As aldosterone concentrates potassium ions into saliva, saliva is naturally the body fluid richest in potassium<sup>8</sup>.

Saliva serves to protect oral tissues in multiple ways. When stimulated, the salivary gland produces a large volume of saliva. The watery nature of saliva cleanses the mouth from bacteria and food debris. Buffering ions in saliva such as bicarbonate helps to neutralize the acid from food and bacteria, protecting the dental enamel against demineralization. Owing to the protective functions of saliva in oral health, patients with chronic dry mouth tend to develop caries and oral infections. Typically, the amount of unstimulated saliva secreted under physiological conditions ranges from 0.4 – 0.5 mL/min. The amount of secreted saliva from 0.2-0.4 mL/min indicates oligosialia, while the amount of saliva less than 0.2 mL/min points to xerostomia<sup>9</sup>.

## Materials and methods

Seventy-two (72) subjects of both genders aged 65-75 were recruited into the study. As there are several variables that affect saliva products, exclusion criteria such as subjects who are smoking, alcoholics, have a history of Sjogren's syndrome, rheumatoid arthritis, lupus erythematosus or have had any surgery on their salivary glands, or have had received radiotherapy in the head and the neck was excluded from the study.

### Sample size calculation:

It is a cross-sectional study, chi-square test was used as a statistical tool for this study.

G\*Power was utilized to compute the minimum sample size for the study archives the power of 0.8 with alpha value 0.05, preferably a large effect size ( $w=0.5$ )<sup>10</sup>. Based on the sample size calculation, a minimum sample size of 32 subjects is required. For this study, we enrolled 72 subjects.

### Statistical Analysis

Data were analyzed by using IBM SPSS Statistics Software for window version 28. A descriptive statistic is expressed as frequency and percentage (%) is used for categorical variables. The Chi-square test is used to test the association between xerostomia and amlodipine with gender and xerostomia with amlodipine. The significance level is set to p-value < 0.05.

### Results

Xerostomia and hyposalivation are generally describing mouth dryness. It is a subjective feeling of dry mouth and can be assessed by asking individuals whether they have such a feeling. To evaluate xerostomia in the present study, an effective intraoral clinical examination was provided with a xerostomia questionnaire.

|         | Xerostomia, n(%) |           | Amlodipine, n(%) |           |
|---------|------------------|-----------|------------------|-----------|
|         | No               | Yes       | No               | Yes       |
| Gender  |                  |           |                  |           |
| Male    | 23 (31.9)        | 16 (22.2) | 15 (20.8)        | 24 (33.3) |
| Female  | 18(25)           | 15(20.8)  | 13 (18.1)        | 20 (27.8) |
| Total   | 41 (56.9)        | 31(43.1)  | 28 (38.9)        | 44 (61.1) |
| p-value | 0.705            |           | 0.936            |           |

**Table 1.** Association of xerostomia and amlodipine with gender.

|            | Xerostomia, n(%) |          |
|------------|------------------|----------|
|            | No               | Yes      |
| Amlodipine |                  |          |
| No         | 22 (30.6)        | 6 (8.3)  |
| Yes        | 19(26.4)         | 25(34.7) |
| Total      | 41 (56.9)        | 31(43.1) |
| p-value    | 0.003            |          |

**Table 2.** Association of xerostomia and amlodipine.

### Discussion

All patients who have taken amlodipine for a duration of more than three years with an age range between 65 to 75 years old have shown xerostomia in variable degrees. The percentage of xerostomia in the medicated

hypertensive group of the present study was higher in males (22 %) than those in females (20 %) which was not significant ( $p = 0.705$ ). However, a statistically significant difference ( $p = 0.003$ ) between amlodipine and xerostomia status was observed, which was higher in males (34.7 %) than that in females (26.4%). Our results are in line with previous reports on elderly populations where elders with systemic disorders and taking xerogenic medications have lower salivary flow rates compared to healthy subjects<sup>11, 12</sup>.

Our analysis of the Chi-square test revealed a relationship between amlodipine and xerostomia amongst the elderly population. Based on the previous reports, a causal relationship between taking amlodipine and having xerostomia as a side effect is highly anticipated. Depending on the individual, different degrees of dry mouth can be the underlying risk to elicit various medical conditions<sup>13</sup>. For instance, decreased salivary production exposes the elderly population to the risk of developing dental caries or oral fungal infections<sup>14</sup>. A persistent decreased salivary production can lead to altered taste and burning mouth sensation. Thinner salivary film in the oral cavity also diminishes the natural defense in the oral cavity against infections such as candidiasis, dental caries, and bacterial sialadenitis<sup>15</sup>. Lesser saliva translates to thinner natural lubricant in the oral cavity, resulting in erythema and mucosal susceptibility to frictional damage from teeth, causing discomfort<sup>16</sup>. Therefore, xerostomia can have a significant impact on a patient's quality of life. Thus, diagnosis and management of xerostomia in the elderly population taking amlodipine has an important clinical implication.

It is important to note that, Dodds et al. works on 2005 studying salivary alterations between healthy and hypertensive subjects showed that the concentrations of albumin, lactoferrin, lysozyme, myeloperoxidase, secretory IgA, and salivary peroxidase were changed in hypertensive subjects' saliva compared to healthy subjects. It is believed that since salivary flow rates were decreased, proteins are concentrated in the depleted fluid volume of saliva, causing subtle changes in the protein concentration<sup>17</sup>. This suggests that not only the quantity of saliva but also the quality of saliva is altered in hypertensive patients<sup>18</sup>.

Furthermore, studies by Navazesh et al.

(1996) that salivary flow rate is affected by seasonal and diurnal factors<sup>19</sup>, for this reason, in our study it was important to standardize the time in the morning (8:00 am -10:00 am) for saliva collection to be considered<sup>20</sup>. Amlodipine was a type of antihypertensive medication, that includes adrenergic blockers, diuretics, ACE inhibitors, calcium channel blockers, and heart glycosides with central effects. Antihypertensive agents are the medication most often associated with the appearance of symptoms compatible with burning mouth syndrome because they can act upon the angiotensin-renin system<sup>21</sup>. Salivary secretion depends on parasympathetic and sympathetic signaling, and parasympathetic activation leads to increased Ca<sup>2+</sup> release and water fluxing out of the cell<sup>22</sup>. Thus, taking a calcium channel blocker such as amlodipine, which acts as a Ca<sup>2+</sup> antagonist, may cause dry mouth by inhibiting the voltage-dependent Ca<sup>2+</sup> channels that are activated by depolarisation to cause resting salivation<sup>23</sup>. Of the worldwide cases of medication-induced xerostomia, 33% were known to be dose-dependent phenomena, as the burning sensation only occurred when the medication dose was increased in pursuit of therapeutic efficacy<sup>24</sup>. Hyposalivation can be caused by various factors such as systemic diseases, the use of medications, radiotherapy of the head and neck, and the use of illicit drugs<sup>25</sup>.

Salivary flow decrease can increase susceptibility to dental caries or oral fungal infections, so these conditions must be given the importance they deserve, antihypertensive drugs can be associated with xerostomia, and several studies have shown the relationship between xerostomia and reduced oral health-related quality of life, especially in the elderly<sup>26</sup>.

## Conclusions

Adverse drug events are normal in the oral cavity and may have a number of clinical presentations such as xerostomia. Xerostomia can cause many implications as saliva helps in maintaining oral mucosa and has a protective function. The signs of adverse drug incidents in the oral cavity should be identified to oral health care professionals.

The current findings indicate that both xerostomia and hyposalivation were prevalent in hypertensive patients who receive medication. Thus, routine monitoring of salivary production in

a hypertensive patient receiving medication can significantly impact patient management. The simplicity of saliva evaluation is convenient, accessible, and reliable in a clinical setting to identify the patient at risk of xerostomia. Once they are identified, available therapeutic strategies can be applied on time to manage xerostomia and hyposalivation. If mitigation has been done and the patient still complains of severe xerostomia, a referral to a cardiologist to change amlodipine to alternate antihypertensive medication can be recommended.

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## Declaration of Interest

The authors declare that they have no conflict of interest.

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