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Review Paper

The use of drugs for the treatment of xerostomia – brief review

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Abstract

Inadequate production of saliva causes an oral imbalance that has a great impact on the individual's quality of life. Diseases of various types are responsible for impaired production of saliva and dry mouth, as happens in xerostomia. It is usually associated with hypofunction of the salivary glands, which shows signs of dryness on oral mucosa, and other morphological features in the oral cavity. Saliva is composed of water and 1% of electrolytes and immunoglobulins, enzymes and other proteins. Its fluid component, which contains ions, is mainly produced by parasympathetic stimulation, while the protein component, produced in the acinar secretory vesicles, is released by sympathetic stimulation. The use of certain drugs is a major cause of xerostomia. Among these we found analgesics, anticonvulsants, antihistamines, antihypertensives, diuretics and antidepressants. The treatment is mainly done by saliva substitutes such as sodium chloride, potassium chloride, monopotassium phosphate and dipotassium phosphate. However, in some cases, stimulants, such as citric acid and sodium citrate, or even topical salivary substitutes can be effective. Furthermore, the use of specific oral care products is well accepted by the patients. The treatment is selected according to the ability of the glands to produce saliva. It is still not fully known what mechanism of action drugs that cause hyposalivation, dry mouth or changes in saliva composition use. Yet, it is important to know the side effects of prescribed drugs.

Keywords: *Drugs; Hyposalivation; Oral Care; Xerostomia*.

1. Introduction

Decreased salivary flow and changes in the composition of saliva can cause a clinically significant oral imbalance manifested by: increased incidence of caries susceptibility to oral candidiasis, burning sensation in the mouth, sore tongue (glossodynia), difficulties with speech, chewing and swallowing, altered taste sensation (dysgeusia) and halitosis [1, 2]. Several diseases of inflammatory, degenerative, infectious and obstructive nature, beyond those caused by neoplastic processes in the salivary glands, culminate in salivary volume dysfunctions, a highly complex problem, often seen in clinical practice. These disorders, if not diagnosed and treated properly, lead to several complications interfering directly with patient`s quality of life. Among them, xerostomia is the most common long-term symptom in most patients [3].
Generally, treatment is done by means of saliva substitutes; however, other modalities of treatment and potential control are under study [4], [5], [6]. These changes in saliva composition have a major impact on the individual's quality of life, as the saliva plays a critical role in two essential human needs, nutrition and communication, and both are committed when there is a dysfunction in salivary production [6], [7], [8], [9]. Therefore, the aim of this review is to highlight morphofunctional and pathophysiological considerations of xerostomia and demonstrate therapeutic components and their mechanisms of action.

2. Functional aspects

Two different groups, the major and the minor glands constitute the system of the salivary glands. The major salivary glands consist of three pairs (parotid, submandibular and sublingual) and the minor salivary glands are about 700 to 900 units present throughout the oral cavity and oropharynx and may also be found in the larynx, trachea and nasopharynx. About 90% of the saliva is produced by the major salivary glands, the remainder produced by the salivary glands of the mucosa of the mouth and pharynx [10], [11].
Saliva is essentially composed of water (99%) and about 1% of organic and inorganic molecules: a variety of electrolytes, such as sodium, potassium, calcium, magnesium, bicarbonate and phosphate; immunoglobulins; enzymes; other proteins and nitrogen products. Protein secretion is subdivided into two types: a serous rich in ptialina (or salivary amylase), responsible for digestion, and other mucosal containing mucin, which is responsible for the lubrication of food. Through the physical properties of adhesion and low resistance to sliding, such a lubrication enables easy swallowing of solid particles and their path through the esophagus [10], [12], [13], [14], [15]. The components of saliva are secreted by independent mechanisms. The glandular tissue is innervated by the autonomic nervous system through fiber from the salivary nuclei (upper and lower). These are located at the junction of the medulla oblongata with the pons, and are closely linked to motor neurons of the glossopharyngeal and facial nerves [16], [17], [18].
In general, the fluid component, which contains ions, is mainly produced by parasympathetic stimulation, while the protein com-

ponent, produced in the acinar secretory vesicles, is released by sympathetic stimulation [17]. Therefore, excitation of both the sympathetic and parasympathetic nerves glands causes stimulation of salivary secretion (an exception, since throughout the body these two systems are antagonists), but the effects of parasympathetic nerves are stronger and more durable [3], [10], [13], [14], [19] whereas the effects of the sympathetic nerves can cause sensation of dry mouth [19], [20], [21].

The excitation of the parasympathetic efferent system determines stimulation of salivary glands, which increases speed in saliva formation, as well as the consumption of oxygen and blood flow [22] and, therefore, is crucial in the regulation of salivary function. The parasympathetic effect may be twofold; on one hand directly stimulating the salivary cells (acinar and tubular) through the close relationship of parasympathetic fibers, causing increased acetylcholine concentration, and the change of electric potential caused by this stimulation; On the other hand, the indirect action increases blood flow, increasing the supply of oxygen, water, electrolytes and substrates for glandular function [23].

Complementary to the parasympathetic system, the sympathetic system stimulates the contractility of the myoepithelial cells by β-adrenergic receptors, resulting in the expulsion of the preformed saliva, transiently increasing saliva flow out through the ducts of the salivary glands excretion; but, soon after, the salivary flow begins to decrease (psialoquese), an effect that is maintained for the length of time that lasts sympathetic stimulation [19], [24]. This second action of the sympathetic is due to the reduced blood flow from the salivary gland produced by sympathetic adrenergic vasoconstriction [25], [26]. Therefore, when there is a sympathetic "over activity", the mouth appears dry and in extreme cases, can yield pain and difficulty in swallowing by the lack of saliva in the oral cavity. The blood flow of the salivary glands is an important modulator of salivary function, and should be suitable for its secretory function [11], [18], [27], [28].

The adaptation of this flow occurs by vasodilators secretion in own salivary glands, when stimulated (i.e: kallikrein, bradykinin). These vaso-controller action would be relatively constant, since the effects of parasympathetic stimulation can persist for long periods. It should be remembered that salivary blood flow is important, since it is formed a rich capillary plexus, which mainly irrigates the ducts, but also the acini, forming arteriovenous anastomoses and saccular veins retention, maintaining high blood pressure during secretory activity; these veins act as blood reservoir, being similar to the cavernosum of the penis system [11], [18], [19], [24], [27], [28].

When the salivary glands become less active with age, a large variation in salivary secretion begins to occur, which can lead to the appearance of many complications. There is no longitudinal study of salivary secretion in the same individual, but some histological changes have been observed and associated with aging, such as degenerative changes: fatty, fibrosis and progressive accumulation of lymphocytes in the salivary glands. The oncocytes, epithelial cells that can be identified by their strong graininess and acidophilia under a light microscope, appears to be a modification of age. Ultra-structural study exhibit an accumulation of altered mitochondria, being found in acini, as well as intercalated and striated salivary gland ducts and may be manifested with the hypofunction of salivary secretion [29], [30], [31], [32].

The protective function of saliva is expressed in several ways. Saliva has a lubricant role, and its glycoproteic content, which makes it mucinous, protects the mucosal lining, forming a barrier against noxious stimuli, microbial toxins and minor trauma. Its fluid consistency also provides a mechanical wash action, which carries non-adherent bacteria and cellular debris from the mouth [30, 33]. Particularly, cleaning promoted by saliva limits the availability of sugar for the microorganisms that cause dental caries. The saliva proteins that bind calcium, helps to form a film, which behaves as a protective barrier [18], [31], [34].

In the digestion, saliva provides taste sensitivity, neutralizes the esophagus content, dilutes the gastric juice, and due to its content of amylase breaks down starch [18], [35], [36], [37], [38]. In gustation, although it allows them to have a sense of satisfaction when the food is experienced, its primary role is the protection, allowing the recognition of harmful substances, as well as being required to dissolve substances to be savored and to carry them to gustatory corpuscles. It also contains a protein called gustina, necessary for growth and maturation of gustatory corpuscles [18], [29], [39], [40], [41].

In addition, antibodies are also present in saliva, being IgA the main immunoglobulin found, having the ability to agglutinate microorganisms. This ability, coupled with the cleansing action of saliva, serves to remove bacteria aggregates [18, 30].

3. Pathophysiology of xerostomia

Xerostomia refers to a subjective sensation of dryness in the mouth and is often, but not always, associated with the hypofunction of salivary glands. It is a common problem, reported in 35% of the elderly, which seems to be the result of medical factors [8], [42], [43]. More than 500 drugs have been reported to cause xerostomia as a side effect, even 63% of the 200 most frequently prescribed drugs in the United States. There are specific drug responsible for producing dry mouth, but the total number of drugs that a person ingests also increases the prevalence of xerostomia [8], [9], [44], [45], [46].

The use of certain drugs is a major cause of xerostomia, but rarely cause irreversible damage to the salivary glands. Among the various drugs that can cause xerostomia the main ones are some types of analgesics, anticonvulsants, antihistamines, antihypertensives, diuretics and antidepressants. Therefore, xerostomia is most common in patients under treatment for mental diseases or hypertension [45], [47].

These drugs have anticholinergic or sympathomimetic properties, acting on muscarinic receptors. Of these receptors, those located in glandular tissues are mainly the muscarinic receptor type 3 (M3), and they are also present in the vessel, the smooth muscle and endothelium [48, 49]. The drugs with this property act by blocking the acetylcholine action on muscarinic receptors. This blocking action of cholinergic function causes the liquid and voluminous part of secreted saliva to be blocked [15], [50].

Some recent drugs, such as omeprazole, protease inhibitors of the HIV virus, tramadol, and new generation of antihistamines can also cause xerostomia [51]. There may be a relationship between the onset or increase of the medication dose and the appearance of symptoms. It is important to note that the reason of the medication use is also relevant. For example, anxious or depressed patients may report symptoms of dry mouth in the absence of drug treatment, which may be a diagnostic complicating factor [52], [53].

Patients with hypofunction of the salivary glands show signs of dryness on oral mucosa. The lips are often cracked, present peeling and may be atrophic. The oral mucosa may have pale and corrugated appearance. In general, the tongue is red and smooth due to loss of buds. Patients may report his lips adhere to teeth and some may observe that the desquamated epithelial cells adhere to the dry glaze [8], [44], [54], [55], [56]. Often, there is a significant increase in tooth wear rates, rapid progression of caries, periodontal disease and aggressive opportunistic fungal infections (especially by Candida albicans and Candida parapsilosis). Moreover, the risk to develop other microbial infections of the oral cavity is also high [56], [57], [58], [59].

4. Treatment

The choice of treatment is based on the salivary gland's ability to produce saliva. If the glandular structure is preserved and active, the gustatory, masticatory or local medicated and/or systemic stimuli usually show some improvement in symptoms [2], [60]. For patients with severe destruction of the glandular parenchyma, salivary substitutes are the most suitable. To check the salivary function, various methods may be employed, being the manual stimulation of the gland and sialometry the simplest. When the

etiological factor is drug, a preventive approach can be used [60, 61]. In cases where the outcome is more favorable, topical salivary stimulants and substitutes can be effective. However, in some cases more specific salivary control maneuvers are required [60], [62]. Salivary stimulants and saliva substitutes are two alternatives and indicating either depends on the severity of the case. Importantly, to have normal production of saliva, the individual must be ingesting an adequate amount of fluids daily [63].

Salivary stimulation can be done through stimulation of oral receptors (afferent) or by direct action on the autonomic nervous system (efferent). The afferent pathway comprises gustatory and masticatory stimulation while the efferent salivary stimulation is pharmacological and hence presents a larger amount of undesirable effects [28], [64], [65], [66]. For gustatory stimulation, may be used ascorbic acid in the form of tablets or solution. However, even promoting a satisfactory increase salivary flow, there are contraindications due to local mucosal irritation, induction of ulcerated lesions and demineralization of tooth enamel with development of hypersensitivity of dentine, pain and risk of systemic infection in the elderly [64], [67].

For masticatory stimulation, chewing gum is recommended as they usually do not have many significant side effects, but it may be noted, in some cases, local irritation and gastric changes when used chronically. The chewing gums promote immediate and lasting increase in salivary flow; one approach widely accepted by most patients [61], [68], [69], [70]. The contraindications of chewing gum are edentulous patients, individuals with ill-fitting dentures, people who have myofascial and/or temporomandibular joint (TMJ) dysfunction, individuals with gastric changes and those who are intolerant to the gum components. A basic precautions for the use of chewing gum is that it should not have sucrose in the composition to prevent the formation of dental caries, because the salivary protective mechanisms are impaired [61], [68], [69], [70].

For the pharmacological stimulation, indicated drugs are secretagogues and disease modifying agents. Among secretagogues, pilocarpine is a parasympathomimetic agent that acts as a partial agonist of muscarinic receptors [61], promotes stimulation of the exocrine glands and therefore promotes salivary secretion, improving the objective component of dry mouth. It is effective in patients without severe destruction of the glandular parenchyma [62]. Several doses and routes for administration of pilocarpine were studied [71], [72], [73], [74], and its most effective dose is 5mg three times daily [75], [76]. Its effect begins about 15 minutes after injection and lasts for about one to four hours [77].

Being a non-selective drug, pilocarpine promotes lot of adverse effects, which appear to be dose-dependent [66]. Such side effects are very common to cholinergic drugs, namely: sweating, headache, increased urination, gastrointestinal disorder, blurred vision, smooth muscle contraction, increased pulmonary secretion and tachycardia [24], [78]. In clinical doses do not appear to be significant effects on the cardiovascular system [64], but their use in cardiac patients with asthma, bronchitis or chronic obstructive pulmonary disease shall be discussed. Contraindications to the use of pilocarpine include cases of iritis or glaucoma by pupillary block and hypersensitivity to components of the formula [79].

As pilocarpine, cevimeline is a sialogogue cholinergic agonist which binds to muscarinic receptors with selectivity for the M3 receptors [62], [80], [81], [82], which leads to a reduction of the adverse effects [61]. By having minimal affinity for cardiac M2 receptor it is better tolerated by patients with cardiovascular problems [82]. Its usual dose is 30 mg three times a day with peak plasma concentrations achieved two hours after ingestion, and half-life of five hours [82], [83]. Side effects of cevimeline are dose-dependent and constitute mainly of gastrointestinal disorders, headache, nausea, sweating and increased urinary frequency [81], [82], [83]. The precautions for the use of pilocarpine, also applies to the use of cevimeline, and contraindications are milder due to the selectivity of the drug [83].

Bethanechol is an analogue of acetylcholine, but resists the action of cholinesterase and therefore has a longer action. Used for patients with postoperative urinary retention or post-partum, is another product studied for patients with hyposalivation. Improves the subjective and objective symptoms of dry mouth in patients taking tricyclic antidepressants or suffering from head and neck radiotherapy [84], [85]. The dose of bethanechol is 25 mg three times daily, increasing to 50 mg three times a day in patients with severe hyposalivation, and it has maximum effect in about an hour after use [62]. Side effects are dose dependent, the most common are: sweating, abdominal discomfort, nausea, diarrhea, headache, lacrimation and bronchoconstriction [62], [84], [85].

Another drug found in some European countries and Japan for the management of dry mouth is the anethole-trithione, which does not have cholinergic action, but increases the availability of muscarinic receptors in the postsynaptic membrane, thus increasing the potential for cholinergic stimulation. [86], [87], [88]. The recommended dose is 25 mg three times daily [89]. Its most frequent side effect is diarrhea and is contraindicated in cases of pregnancy and lactation, patients with jaundice, cirrhosis and obstruction of biliary tract due to its hepatic metabolism [90]. A clinical trial was conducted with this drug to verify the efficacy in patients with hyposalivation showing increased salivary flow, reduced xerostomia and fewer gastrointestinal effects [89], [91].

Some clinical trials have been performed with mucolytic drugs such as bromhexine, to prove its effectiveness in salivary flow, but the results have been controversial [62]. The bromhexine is a mucolytic that acts by decreasing the viscosity of mucous secretions and is contraindicated for patients lactating, pregnant women and patients with active peptic ulcer. Studies found that its use for the treatment of xerostomia in patients with Sjögren's syndrome showed no significant difference to placebo [92].

One of the treatments better accepted by patients includes the use of specific oral hygiene products in toothpaste, mouthwash, gel and spray [93]. In a double-blind crossover randomized study conducted by Lopez and colleagues [61] with 30 patients, the use of two oral care products in diagnosed (at least three months) patients with xerostomia was compared. The results showed an improvement of the symptoms of oral dryness for both products, wherein the product based to triclosan, fluorine, vitamin E, enoxolone, provitamin B5 and excipients for xerostomia showed greater antimicrobial action on bacteria causing caries when compared to products based on enzymes, salivary substitutes and fluorine. The main objectives for these products are: stimulating salivary flow, replacement of salivary content, prevention of complications arising from xerostomia and the treatment of these [93], [94], [95].

Among the salivary substitutes, the most used are sodium chloride, potassium chloride, monopotassium phosphate and dipotassium phosphate. The group formed by chloride and phosphate has a direct effect on the composition and quality of saliva and fluids present in the oral cavity, aiding isotonic maintenance by the action of chlorides and rebalancing the salivary pH done by phosphates [67], [96]. These substances additionally form a protection and improve the integrity of the oral cavity mucosal lining and prevent demineralization of tooth enamel [21], [66].

In the group of salivary flow stimulants, citric acid and sodium citrate are the most used. The presence of sodium citrate prevents ambient acidity thereby protecting against demineralisation together with citric/citrate as stimulating effective and safe for maintaining the integrity of dental enamel. Already citric acid is a natural sialogogue drug that stimulates the taste buds through parasympathetic efferent pathways [97]. Its application in the apex of the tongue causes salivary secretion both the submandibular and sublingual glands as the parotid, while causing a burning sensation similar to that caused by exposure to capsaicin. Salivary secretion is also observed after application of citric acid on the tongue base, more precisely in vallate papillae, whose response was associated with a bitter taste [97]. Gjorstrup (1980) [98] provide evidence to show that citric acid causes a reflex activation of the sympathetic nerves, parasympathetic besides, when administered orally to rabbits. In another study, Femiano and colleagues (2011) [99] found that citric acid has proved effective against dry mouth in a concentration of 3%, giving a beneficial effect 15 minutes after

application and long term in relieving the sensation extending by 1 hour after its use.

Only local side effects, that can be avoided, have been reported for the citric acid in mouthwashes (e.g., erosion of tooth enamel), making it potentially safer than treatment with muscarinic agonists [28], [100], [101]. The use of citric acid in mouthwashes for long periods therefore requires continuous dental monitoring and some essential behavior of recommendations, such as restricting the contact time with the surface of the tooth, do not brush the teeth for at least 1 hour after using the product, limit or eliminate other substances responsible for tooth erosion from the diet (spicy or acidic foods, soft drinks, alcohol, carbonated mineral water, fruit juice, etc.), and mouthwash with sodium bicarbonate solution in water to increase the oral pH [99].

Triclosan is a nonionic mouthwash of broad spectrum covering Gram-negative and Gram positive bacteria, viruses and fungi, being safe for use in humans. Its action not only affects those microorganisms attached to the tooth, as other oral sites, such as tongue and lining mucosa. Qualitative and quantitative changes in the formation of dental plaque have been proven with the use of triclosan [60]. It has been demonstrated the in vitro effect of triclosan on the thickness reduction of dental plaque. There was also a reduction in the number of anaerobic bacteria and Actinomyces in dental plaque after use for 21 days triclosan [102]. Moreover, it has beneficial effects in reducing gingival inflammation. In vitro studies have shown direct anti-inflammatory effect of triclosan on gingival inflammation, through the inhibition of arachidonic acid metabolism pathways leading to the production of known chemical mediators of inflammation such as prostaglandins (PGE2), leukotrienes and lipoxins [103], [104].

Chlorhexidine is a biguanide positively charged and is highly interactive in anions of the oral cavity. It has bactericidal and fungicidal effectiveness in the oral environment, and safe use in humans and has demonstrated clinical efficacy in a wide scientific literature. In oral hygiene products the most used concentrations are 0.12% and 0.2% [61], [96], [105], [106].

Fluoride mechanism of action to combat tooth decay is based on its constant presence in the oral cavity reducing the amount of lost minerals, it occurs with a decrease in pH and demineralization of tooth structure [107], [108]. Furthermore, when the pH returns to normal saliva naturally tries to restore the lost tooth minerals, being this property activated by the presence of fluoride in suitable concentrations [107].

The stimulation of salivary flow triggered by the use of xylitol increases simultaneously the levels of all the natural mechanisms of saliva [72], [73]. The anticariogenicidade, one of the most important properties of xylitol is mainly determined by the non-fermentation by bacteria of the genus Streptococcus, whose proliferation in the oral flora then becomes limited. This leads to decrease in the amount of insoluble polysaccharides and increases soluble polysaccharides, resulting in a less adherent plate and easily removed by normal tooth brushing [109], [110].

Vitamin E (tocopherol) is present in the form of alpha-tocopherol in oral hygiene products. Its pharmacodynamics is based on their property to prevent cellular oxidation with anti-inflammatory effects. This effect, due to increased cytological resistance in the epithelium of the mucosal lining of oral cavity, provides an improvement in gingival blood flow and a faster healing of ulcerated oral lesions [111], [112], [113].

Aloe vera extract is obtained from the plant species called Aloe barbadensis. Medicinal properties have been attributed to active components of their extracts as anthrone, chromone, verasin aloe and hydroxyaloin [114]. Examples of phenolic antioxidante of common plants include cinnamic acid derivatives, coumarins, flavonoids, polyfunctional organic acids and tocopherols [115]. Davis et al (1989) [116] demonstrated healing wound properties of A. barbadensis and an effective anti-inflammatory, cinnamoyl-C-glucosyl-chromone, was isolated from the same plant [117].

When used on the gingival tissue and the oral mucosa lining, panthenol (provitamin B5) is converted to pantothenic acid, which is an essential element in the synthesis of lipids, proteins, and the strength of the gingival and the oral mucosal lining collagen fibers. Provitamin B5 stimulates cell proliferation and helps the healing of inflamed areas [66], [118]. Enoxolone (potassium glycyrrhizinate) is an active ingredient obtained by hydrolyzing the plant extract of "Glycyrrhiza glabra", known for Licorice name. From this plant are obtained for therapeutic purposes various effective drugs such as cicatrizing and anti-inflammatory. The enxolona (potassium Glicirrinato) is an active ingredient obtained by hydrolyzing the plant extract of "Glycyrrhiza glabra", known for Licorice name. From this plant are obtained for various purposes such as therapeutic drugs effective cicatrizing and anti-inflammatory. This action contributes to improving the general conditions of the gingival epithelium, which reduces inflammation and bleeding, characteristic signs of periodontal disease in patients with xerostomia [78], [119], [120].

For xerostomic patients with oral candidiasis is indicated the use of topical antifungal agents such as miconazole or nistanina three times a day for 15 days. In refractory cases or when the patient is immunocompromised, it becomes necessary to use systemic antifungal agents such as fluconazole 100mg, once a day for ten days, or ketoconazole 200 mg twice a day for two weeks [120].

5. Conclusion

Xerostomia is an oral amendment that causes many complications for patients and can be triggered secondary to the use of certain medications. It is unclear what mechanism used for psychotropic drugs to induce hyposalivation, xerostomia or changes in the composition of saliva, because there are many other receptors of the endogenous substance in the salivary glands that mediate salivary flow, such as substance P and vasoactive intestinal peptides receptors. However, it is essential in the practice of drug prescriptions the knowledge of drug interactions and side effects of prescribed drugs. Many highly complex changes may not mean a primary pathological condition, but secondary to the use of drugs.

The treatment of xerostomia can be based on the use of systemic drugs, such as secretagogues, and the use of specific oral hygiene products. The use of secretagogues, however, must be evaluated with caution, mainly due to the possibility of side effects and still develop drug interactions with other drugs the patient may be taking. Alternatively, the use of oral hygiene products containing triclosan, vitamin E, aloe vera, enxolona, fluoride, xylitol, salivary substitutes and salivary stimulants is effective in improving patient`s quality of life, with still presenting a potent antimicrobial action against bacteria that cause decay.

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