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Review Article

Pharmacodynamic Causes of Xerostomia in Patients on Psychotropic Drugs

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Abstract

Xerostomia is the sense of dry mouth which may results from reduced salivary flow. Since saliva plays a key role in the oral homeostasis, major oral health issues and decreased quality of life reflect xerostomia in patients. Xerostomia represents significant burden among patients on pharmacotherapy. One of the frequently used drugs which induce xerostomia are psychotropic drugs. This article summarizes major pharmacodynamic interactions of psychotropic drugs with signalling mechanisms involved in salivary secretory processes.

Keywords: Xerostomia; Psychotropic Drugs; Benzodiazepines; Antidepressants; Antipsychotics

Introduction

Oral homeostasis is highly dependent on the presence of saliva. Roles of saliva are numerous: bolus formation, initiation of food digestion, sense of taste and speech as well as protective role [1]. Namely, by forming a protective mucin layer, saliva protects oral cavity acting as lubricant, and reduces friction between contact surfaces of teeth and dentures [2,3]. Ever since the study of Fox., *et al*. it is well known that alterations in secretion of lubricating mucins had the strong impact on xerostomia sensation especially under circumstances of xerostomia associated with unchanged salivary flow [4]. Saliva is crucial in dental decay prevention, antimicrobial protection and protection of oral tissues from oxidative stress [5,6]. Thus, the salivary gland dysfunction may lead to diminished intraoral tissues protection against infection and injuries, altered mastication, taste and swallowing, disturbance in speech and dental prosthesis wearing, significantly affecting quality of life of patients [7-11]. Salivary secretion is principally regulated by autonomic nervous system: parasympathetic, through acetylcholine (ACh)-induced activation of muscarinic M_3 receptors (production of copious saliva with water and electrolytes), and sympathetic, through norepinephrine and epinephrine-mediated activation of alpha 1-adrenoceptors (production of water and electrolytes-rich saliva), and beta-adrenoceptors (production of viscous, amylase- and mucin-rich saliva) [12]. Stimulation of muscarinic M_3 and adrenergic alpha-1 receptors causes inositol phospholipid turnover and inositol triphosphate release with consequent increase in intracellular Ca^{2+} while stimulation of beta- adrenoceptors leads to an increase in intracellular cyclic AMP (cAMP) mediated by activation of adenylcyclase [12]. Elevation of intracellular cAMP is linked to secretion of salivary proteins stored in secretory pools bound to membrane [12]. Beside autonomic nervous system, significant role in regulation of salivary glands function have neuropeptides such as tachykinins (substance P, neurokinin A, neuropeptide Y) and autocoid - bradykinin [13,14].

Xerostomia- causes and evaluation

Drugs are considered to be the most frequent cause of oral dryness. More than hundred drugs were associated with this condition, considered oral dryness to be their oral adverse reaction. Among them, of most importance are frequently used antihistaminic drugs, antihypertensives and psychotropic drugs [15]. Beside drugs, other health conditions, such as autoimmune disorders, endocrine disorders or radiation therapy comprise the major causes for dry mouth. When describing the oral dryness, the term xerostomia is used to express the subjective sensation of oral dryness, while the term hyposalivation expresses the actual decrease in salivary flow rate [16].

Psychotropic drugs	Partial list of drugs
Benzodiazepines	Diazepam, Lorazepam, Alprazolam, Temazepam
Antidepressants: SSRIs, SNRIs	Venlafaxine, Duloxetine, Sertraline, Fluoxetine
Tricyclic antidepressants	Amitriptyline, Imipramine
Antipsychotics	Phenotiazine, Clozapine, Risperidone, Lithium

Table 1: Partial list of psychotropic drugs that cause dry mouth.

SSRIs: Selective Serotonin Reuptake Inhibitors; SNRIs: Selective Norepinephrine Reuptake Inhibitors.

Investigating the xerostomia, an interview is the method of choice for data collection, comprises various types of questions and responses (qualitative or quantitative), used to describe frequency, duration and degrees of dry mouth, as well as its impact on every-day life. Most frequently, a single question is used in order to describe xerostomia: question "Does your mouth usually feel dry?" combined with Yes/No answers [17-18]. On the other hand, Flink., *et al.* (2005), used six variables associated with salivary gland function ("difficulty experiencing in speaking due to dryness"; "difficulty experiencing in swallowing due to dryness"; "how much saliva there is in your mouth"; "dryness of throat"; "dryness of lips"; "consistency of saliva") which were rated using Visual Analog Scales [19].

Measurement of salivary flow rate, as objective indicator, usually is defined by estimation of unstimulated whole saliva flow rate (UWSFR) or stimulated whole saliva flow rate (SWSFR). Method of collection of saliva from individual comprises "draining", "spitting", "suction" or "swab" methods, during 5, 10 or 15 minutes, and expression of the amount of obtained saliva in volume or weight units. Depending on whether unstimulated whole saliva (UWS) or stimulated whole saliva (SWS) was collected, aforementioned methods have different suitability degree [20]. It has been proved that "suction" and "swab" methods are not suitable for UWS collection because the process itself can stimulate saliva secretion [20]. "Draining" method is not accepted in patients because of the unpleasant feeling during collection [17,20,21]. The most frequently used method for UWS collection is "spitting" method, which has been proven to be the most suitable, especially for UWS collection in cohort studies [22,23]. When collecting SWS, "spitting" method is most commonly used in combination with paraffin wax or gum base chewing or application of citric acid for saliva stimulation [22]. If UWSFR is below 0.1 ml/min and SWSFR- less than 0.7 ml/min, salivation is considered as very low, if UWSFR is between 0.1 and 0.2 ml/min and SWSFR- between 0.7 and 1.0 ml/min it is rated as low, and if UWSFR is above 0.2 ml/min and SWSFR- above 1.0 ml/min it is considered as physiologic [18,19].

Treatment of xerostomia

Xerostomia could be relieved by wetting the oral mucosa by using substitutes for saliva which contain mucin, glycerin or carboxymethylcellulose, hydroxypropyl cellulose or hydroxyethyl cellulose. However, artificial saliva, although exerting the physical characteristics of saliva does not have any antimicrobial properties. It is noteworthy to encourage patients to regularly practice oral and dental hygiene, to avoid sugar, acidic or spicy foods and to stop smoke and use alcohol.

Benzodiazepines and dry mouth

Benzodiazepines (BDZ) are anxiolytic and sedative drugs, with effects mediated by BDZ receptors [24]. These drugs are widely used in the dentistry for oral and intravenous sedation. BDZ receptors are classified into a central- type, linked to $GABA_A$ receptor containing chloride channels and peripheral-type not linked to $GABA_A$ receptor, both receptors are found to be present in brain as well as in salivary glands [25]. Clinical trials in humans point at benzodiazepines as the cause of mild to serious oral dryness [24] Studies in rat salivary glands showed that BDZ inhibit muscarinic receptor- stimulated salivary output as well as the release of amylase acting through both type of BDZ receptors [26,27]. In rat parotid cells, Kujirai., *et al*. have shown that diazepam through BDZ receptors decreased inositol 1,4,5-triphosphate and $[Ca^{2+}]$, signaling molecules involved in muscarinic and alpha-1 adrenergic-mediated salivary secretion [28].

Antidepressants and dry mouth

Prevalence of xerostomia among patients under antidepressants is being significantly more often reported in patients taking the conventional, tricyclic antidepressants (70 - 85% of patients) compared to patients under novel drugs of selective serotonine reuptake inhibitors group (15 - 35% of patients) [29-32]. Tricyclic antidepessants (TCAs), such as amitriptiline or imipramine, block the reuptake of both noradrenaline and serotonine into the nerve terminals and therefore enhance norepinephrine- and serotonin-mediated transmission. In addition, these drugs also have affinities for muscarinic, alpha-adrenergic and histamine H1 receptors, accounting for their most common side effects such as: dry mouth, postural hypotension or sedation, respectively. Investigations in humans and animals showed that TCAs by various mechanisms including: inhibiting muscarinic- [29,33], alpha- adrenergic receptors' function [34], by decreasing number and transductional signal underlying beta- adrenoceptor stimulation [35] lead to alterations in salivary output and composition [36]. Selective serotonin reuptake inhibitors (SSRIs), such as fluoxetine, selectively inhibit the reuptake of serotonin and have little affinity for muscarinic or histamine receptors therefore induce less pronounced xerostomia [29,32]. Concerning mechanism of possible inhibitory effects of SSRIs on cholinergic-induced salivation, it is noteworthy that most recent investigations in brain have shown that fluoxetine increases activity of acetylcholinesterase, enzyme that metabolize ACh, and therefore decreases ACh-mediated transmission in brain [37].

It is interesting to note that antidepressants have opposite effects on unstimulated and stimulated salivary flow on rat model [38]. Namely, imipramine (TCAs) decreases, while fluoxetine (SSRIs) only presents tendency to decrease unstimulated salivation in rats, while both antidepressants are shown to increase muscarinic receptor-stimulated salivation with no significant alteration in total protein or amylase levels [38].

Antipsychotics and dry mouth

Antipsychotics are used for schizophrenia treatment and exert strong inhibiting effect on dopamine D_1- and D_2 -receptors (older, typical antipsychotics) or less robust, selective dopamine D_2- combined with serotonine $5HT_2$- receptors blockade (new, atypical antipsychotics). Since typical antipsychotic medications, such as chlorpromazine or haloperidol, have affinity for muscarinic-, histamine H_1- or alpha 1- receptors, also, their use is followed by frequently reported xerostomia [39]. Atypical antipsychotics, such as clozapine or olanzapine, exhibit D_2 - receptor selectivity, but have less significant affinity for histaminergic, muscarinic and alpha adrenergic receptors, also [40]. Investigations on patients and animals showed that atypical antipsychotics produce less frequently dry mouth than typical antipsychotics [41,42]. In an experimental model of rat, clozapine and olanzapine were able to exert both agonistic and antagonistic effects on salivary secretion [43,44]. Antagonistic effects on secretion of these drugs were shown to be the result of inhibition of muscarinic M_3 and alpha1 adrenergic receptors by reducing the parasympathetically- and sympathetically-stimulated salivary flow. Agonistic effects of clozapine and olanzapine are mediated by muscarinic M_1 and neurokinin receptors in rat, respectively, producing low-level and long-lasting salivation, not related to stimulatory activity [42-44]. These results support the hypothesis of dominating stimulatory effects of clozapine at rest and during the night and dominating inhibitory effects in states of increased secretory demands [44].

Lithium and dry mouth

Lithium is mood- stabilizing drug that acts via interference with phosphatidyl inositol pathway. Namely, Saiardi and Mudge showed *in vitro* that lithium regulate the rate of phosphoinositide synthesis in neurons [45]. Also, in rat submandibular gland, Popović., *et al*. showed that chronic lithium treatment significantly decreased salivation induced by muscarinic- and alpha1- receptors (activation of both involving production of phosphatidyl inositol 1,4,5-triphosphate as a second messenger), but not by beta-receptors (activation of which involves production of cyclic AMP) [46]. Beside this cellular mechanism, other factors associated with lithium therapy may contribute to decreased salivary function, such as the prominent polyuria as the result of inhibition of action of antidiuretic hormone in kidney (diabetes insipidus). One of the most common side effects during long-term lithium treatment is xerostomia reported in majority (> 70%) of patients [47].

Conclusion

Xerostomia represents significant complain among patients on pharmacotherapy with psychotropic drugs. In most cases, xerostomia is the result of psychotropic drug- interference with receptor(s) or signalling mechanisms involved in salivary secretion. Impaired salivation cause difficulties in tasting, chewing, swallowing, and speaking while increasing the chance of developing dental decay, tooth sensitivity and oral infections. Patients on therapy for depression, bipolar disorder, schizophrenia or anxiety may suffer from mild oral discomfort or major oral disease due to xerostomia resulting in compromised patient's health and quality of life.

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