Established and Novel Approaches for the Management of Hyposalivation and Xerostomia

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Abstract: Hyposalivation, often symptomatically manifested as xerostomia (dry mouth sensation) may indicate the presence of altered salivary gland function and places patients at a higher risk for oral complications. Diverse symptoms and consequences have been associated with hyposalivation, such as difficulties with speaking, swallowing and tasting and a significant increase in dental caries and other oral infections. Although hyposalivation may be caused by a variety of conditions (head and neck radiotherapy, Sjögren’s syndrome, medications, etc.), its hallmark symptom, xerostomia, is common to all such disorders, and varies only in intensity. Therefore, treatment is generally non-specific, and similar therapeutic approaches are used in all cases.

In the present paper, available palliative oral care in the form of saliva substitutes, such as mouthwashes or gels, is detailed. Also salivary flow stimulants, such as certain pharmaceutical or gustatory preparations, acupuncture and electrostimulation are reviewed. Finally, other approaches, currently under investigation, such as biological and gene therapies, are discussed. The degree of evidence of the best known methods and their intended use are analyzed.

Keywords: Hyposalivation, xerostomia, dry mouth, mouthwashes, pilocarpine, cevimeline, acupuncture, electrostimulation.

INTRODUCTION

Saliva is essential for the maintenance of well-being and oral health. Saliva enables the proper and comfortable performance of oral functions, such as speech, swallowing and tasting. It protects the oral structures (teeth, soft tissues) from mechanical, microbial and chemical insults which continuously threaten the oral integrity. In order to fulfill this role, a normal quantity and composition of saliva need to be secreted by the salivary glands.

The function of salivary glands is frequently impaired by a variety of pathological conditions, the most prominent being autoimmune diseases, head and neck radiotherapy and adverse effect of numerous medications. This results in hyposalivation, and, as a consequence, the affected individuals usually suffer from xerostomia, a symptom whose impact in quality of life ranges from distress to devastation. Patients may experience dysarthria, dysphagia, dysgeusia and sleep disturbances. Individuals with salivary gland dysfunction are liable to caries, dental erosion, glossitis, gingivitis, Candida infections of the mouth and acute suppurative sialadenitis [1].

The management of oral dryness remains a significant clinical challenge. Increasing secretion of natural saliva should not only lead to the relief of xerostomia, but also to maintaining oral health as saliva contains essential anti-cariogenic and anti-infective factors [2]. However, there is no general agreement about a salivary flow rate value that distinguishes between “normal” and “abnormal” [3]. Thus, treatment is principally directed towards lessening the sensation of oral dryness and prevention of disease of the oral tissues (particularly the teeth and gingivae) [4]. There have been many attempts to reach a consensus about the most efficient treatment of hyposalivation, however the conclusions were mostly ambiguous [5,6,7,8,9]. Adding to this difficulty is the fact that often the patients’ health is already compromised by concomitant diseases and medication intake, making the gamut of therapeutic choices narrow.

The aim of this review is to present the range of available treatments for patients suffering from hyposalivation. It deals with the diversity of alternatives, covering topical preparations, systemic medications (pilocarpine, cevimeline and other salalogues), acupuncture and electrostimulation. Also methods under investigation are discussed, such as biological and gene therapies.

TOPICAL PREPARATIONS

Worldwide, salivary substitutes are probably the mainstays of therapy of longstanding oral dryness. There are increasing numbers of agents being developed for the potential management of xerostomia, particularly that of salivary gland dysfunction associated with radiotherapy of the head and neck or Sjögren’s syndrome (SS). The majority of the salivary substitutes are based upon carboxymethylcellulose (CMC) [10], hydroxyethylcellulose (HEC) [11], polyglyceryl methacrylate (PGM) [12], hydroxypropylcellulose (HPC) [13] or animal mucin [14,15], although preparations based upon glycerol [16], canola oil [14], olive oil, linseed extract [17], oxygenated glycerol triester(s) [18], prophylin [19], xanthan gum [20,21] have been developed. Some of these preparations contain fluoride (e.g. Saliva Orthana®), based upon CMC although it is not known if this has any genuine anti-caries effect. The majority are pH neutral but some are acidic (e.g. Glansor®), Saliva Natura® and Salivix® and have the potential, but unproven risk, to increase dental erosion. Clearly, preparations containing sugar should be avoided to prevent the possibility of accelerating caries in patients already at risk due to their dry mouth. Present evidence indicates that no one of the aforementioned agents is definitively better than another and while they all may reduce some aspect of the symptom of xerostomia, usually associated with radiation-associated salivary gland destruction or SS their long term benefits with regard to oral or systemic wellbeing have not been demonstrated [22].

A number of moisturising oral gels are available for xerostomia based on HEC, olive oil and betaine (Xerostom®), HPMC (Biotene Oral Balance gel®) or whey extract and aloe vera (BioXtra®). These agents are usually applied on a regular basis to the oral mucosa, although they may also be delivered via an intra-oral device [23]. Regardless of the mode of delivery, the gels may lessen symptoms of xerostomia, but salivary gland function, as expected, is not altered [22].

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Gums of various types (e.g. containing xylitol/sorbitol, Freedent® or V6®) can lessen symptoms of xerostomia, presumably due to a topical (gustatory) or a mechanoreceptive/proprioceptive (masticatory) action, although there is no consistent evidence that the gums are notably better than salivary substitutes and cause a significant increase in salivary flow [22]. This may be due to the fact that gums are effective only if there is remaining salivary functional tissue. Thus, after testing if salivary flow rate increases after stimulation, one may make a choice whether to stimulate or use a saliva substitute. Nevertheless, there is evidence that xylitol-based products may decrease dental caries incidence [24].

Toothpastes (e.g. Xerostom®, Biotene®) supposedly designed for the treatment of dry mouth and sometimes used as part of a mouthcare system with gels and mouthwashes may subjectively improve xerostomia and symptoms allied to oral dryness but do not improve salivary gland function [22]. Aside from fluoride some of the mouthrinses and gels contain supposed antimicrobial agents, for example the Biotene® preparations contain glucose oxidase, lactoperoxidase, lactoferrin and lyzosyme, and the BioXtra® preparations lactoperoxidase, lactoferrin, lysozymes and immunoglobulins [25]. There are however limited data as to the precise in vitro or in vivo antimicrobial effects of these agents although they may each have an in vitro inhibitory action against Streptococcus mutans and Lactobacillus acidophilus but no action against Candida albicans [25]. It has been reported that a mouthwash based upon linseed oil (Salium®) may reduce levels, but does not change the constituents of intra-oral supragingival plaque [17,26].

A detailed systematic review of topical therapies for the management of dry mouth has recently been published [22]. It is evident that while there is a wide spectrum of available therapies, few have been examined in well planned, appropriately powered studies that ensure no bias. These agents do seem to cause a lessening of symptoms of xerostomia, that may in turn improve quality of life - but their long-term impact upon oral and systemic well-being are presently not objectively demonstrated. Until the necessary research is undertaken patients should still be provided with such agents, but be advised of their limitations for the treatment of dry mouth. The present literature indicates that no one topical agent is better than another [27] and there are no data as to the long-term compliance of patients provided with such agents.

PILOCARPINE

Pilocarpine is a cholinergic parasympathomimetic agent acting primarily as a non-selective muscarinic agonist, but it also possesses mild beta-adrenergic stimulating properties. Pilocarpine increases salivary secretion by direct stimulation of salivary muscarinic receptors on the acinar cell surface. The increased secretion leads to greater moisture of the oral mucosa and reduction of dry mouth complaints. For pilocarpine to be an effective secretogogue, some remaining functional salivary tissue must be present.

In 1986, an initial report of use of pilocarpine for relief of xerostomia and increase of salivation in subjects with salivary gland dysfunction was published [28]. Subsequently, there have been a number of adequately powered, well-controlled, randomized clinical trials (RCTs) examining the effects of pilocarpine in subjects with oral dryness complaints associated with SS and post head-and-neck radiotherapy. Pilocarpine has been shown to be effective in relieving complaints of dry mouth in both conditions, with acceptable side effects, at oral doses of 5-7.5 mg given three or four times daily. Regulatory approval has been granted for this indication in many countries.

At least nine RCTs have been reported in subjects who complained of oral dryness and had reduced salivary flow following head-and-neck radiation. Results of two of these are of particular interest due to their size and design (Table 1) [29,30]. These, as well as other smaller trials, demonstrated that pilocarpine was more effective than placebo treatment and that approximately half of the patients will benefit from oral pilocarpine treatment post-radiotherapy. While there have been extensive clinical reports of pilocarpine use in SS, there are two larger placebo-controlled, RCTs (Table 1) [31,32]. These have demonstrated significant improvement in xerostomia with pilocarpine versus placebo. In general, symptomatic improvement was noted within a few weeks of initiation of treatment, although in some cases this was not seen until 12 weeks. Following oral dosing, acute effects were noted for 1-3 hours, with a gradual diminution in secretion; however, an overall, persistent improvement in dryness symptoms was reported with continuing therapy. There have been no reports of either improvement in underlying salivary function with chronic use of or development of resistance to the stimulating properties.

Eleven RCTs have investigated a possible beneficial protective effect on salivation for administration of pilocarpine during a course of head-and-neck radiotherapy. Findings have been inconsistent and it would appear that there is, at best, only a modest benefit to use of this agent during radiotherapy.

In all patient groups, side effects were frequent but generally mild and most commonly include: sweating, warmth or flushing (especially on face and neck), chills, fever, increased urgency or frequency of urination, lacrimal and nasal secretion, joint pain, muscle aches and pains, unusual tiredness or weakness, mild gastrointestinal tract distress, diarrhea, cramping and nausea.

Often mentioned contraindications to the use of pilocarpine, which must be discussed with the prescribing doctor, include: asthma, acute iritis, glaucoma, chronic bronchitis or another type of chronic obstructive pulmonary disease, kidney stones, gallstones, gallbladder, heart, or liver disease.

CEVIMELINE

Cevimeline is a cholinergic agonist that binds with M3 muscarinic receptors on salivary and other exocrine glands [6]. A number of RCTs studies have evaluated the clinical effect of cevimeline in patients suffering from dry mouth, two of them (the largest among the studies on SS patients and another testing cevimeline on post-radiation patients) are presented in (Table 1). The studies generally show that therapy with cevimeline, 30 mg 3 times daily, provides substantive relief of xerostomia symptoms in patients with SS [33,34,35,36]. The drug was generally well tolerated, with expected adverse events (AEs) resulting from its muscarinic agonist action, such as sweating, cephalgia, nausea and dyspepsia, sinusitis, infections of the upper respiratory system, rhinitis and diarrhea [37].

A non-controlled study assessing the effects of cevimeline 45 mg t.i.d. given during 52 weeks to 255 patients suffering from radiation-induced xerostomia showed, utilizing a global efficacy evaluation, that cevimeline improved dry mouth in most subjects (59.2%) [38]. However, 18 subjects (7.1%) had at least one serious AE. The studies generally show that therapy with cevimeline, 30 mg 3 times daily, provides substantive relief of xerostomia symptoms in patients with SS [33,34,35,36]. The drug was generally well tolerated, with expected adverse events (AEs) resulting from its muscarinic agonist action, such as sweating, cephalgia, nausea and dyspepsia, sinusitis, infections of the upper respiratory system, rhinitis and diarrhea [37].

Often mentioned contraindications to the use of pilocarpine, which must be discussed with the prescribing doctor, include: asthma, acute iritis, glaucoma, chronic bronchitis or another type of chronic obstructive pulmonary disease, kidney stones, gallstones, gallbladder, heart, or liver disease.
OTHER PROPOSED SYSTEMIC SIALOGUES

There have been a large number of agents proposed as systemic therapeutics for relief of xerostomia and stimulation of salivation. However, it should be recognized that, at this time, only pilocarpine and cevimeline have been approved for relief of dry mouth symptoms in humans and have undergone extensive, controlled clinical trials. The other drugs listed are not approved for human use for this indication and have varying degrees of clinical evidence. The discussion to follow focuses on those that have the most robust clinical testing.

Anetholetrithione

There have been a limited number of clinical trials utilizing anetholetrithione as a salivary stimulant for xerostomia. The results have been mixed and suggest, at best, a modest response [39]. There have not been adequately sized or controlled trials with this agent.

Bethanechol

Bethanechol is a choline ester with muscarinic agonist properties. It is approved for treatment of acute postoperative and postpartum nonobstructive (functional) urinary retention and for neurogenic atony of the urinary bladder with retention. It also stimulates gastric motility, increases gastric tone and may restore impaired rhythmic peristalsis. Bethanechol has been evaluated in a number of clinical trials for treatment of xerostomia, mostly in the post-head- and-neck-radiation period. Generally, responses have been encouraging, although trials of sufficient size have yet to be conducted. Increases in salivary output have been noted, along with improve-

<table>
<thead>
<tr>
<th>Agent and dose tested</th>
<th>Study reference</th>
<th>Control</th>
<th>Sample tested</th>
<th>Follow-up period</th>
<th>Xerostomia severity</th>
<th>Salivary flow-rate</th>
<th>Adverse effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pilocarpine 5.0; 10 mg t.i.d.</td>
<td>Johnson et al, 1993 [29]</td>
<td>Placebo</td>
<td>Post-head and neck radiation</td>
<td>207</td>
<td>12 weeks</td>
<td>VAS</td>
<td>5 mg improved p=0.003</td>
</tr>
<tr>
<td>Pilocarpine 2.5; 5.0; 10 mg t.i.d.</td>
<td>LeVeque et al, 1993 [30]</td>
<td>Placebo</td>
<td>Post-head and neck radiation</td>
<td>162</td>
<td>12 weeks</td>
<td>VAS</td>
<td>Tendency of improvement p=0.057</td>
</tr>
<tr>
<td>Cevimeline 15; 30 mg t.i.d.</td>
<td>Witsell et al, 2012 [37]</td>
<td>Placebo</td>
<td>Post-head and neck radiation</td>
<td>54</td>
<td>6 weeks</td>
<td>Xerostomia grade 1 or 2</td>
<td>Improvement not different than placebo</td>
</tr>
<tr>
<td>Pilocarpine 2.5; 5.0 mg q.i.d.</td>
<td>Vivino et al, 1999 [31]</td>
<td>Placebo</td>
<td>1yr and 2yr SS</td>
<td>373</td>
<td>12 weeks</td>
<td>VAS</td>
<td>5 mg improved p=0.001</td>
</tr>
<tr>
<td>Pilocarpine 5.0; 7.5 mg qph</td>
<td>Papas et al, 2004 [32]</td>
<td>Placebo</td>
<td>1yr and 2yr SS</td>
<td>256</td>
<td>12 weeks</td>
<td>VAS</td>
<td>Improved p=0.001</td>
</tr>
<tr>
<td>Cevimeline 15; 30 mg t.i.d.</td>
<td>Petrone et al, 2002 [33]</td>
<td>Placebo</td>
<td>1yr and 2yr SS</td>
<td>197</td>
<td>12 weeks</td>
<td>VAS</td>
<td>30 mg improved p=0.0004</td>
</tr>
<tr>
<td>Intraoral electrostimulator 10 min at a time, frequency at subjects discretion</td>
<td>Strietzel et al, 2007 [48]</td>
<td>Sham device</td>
<td>Mixed</td>
<td>114</td>
<td>4 weeks</td>
<td>VAS</td>
<td>Improved p&lt;0.002</td>
</tr>
</tbody>
</table>

Legends:
SS: Sjögren’s syndrome
VAS: visual analogue scale
SAE: serious adverse events
ment in dry mouth symptoms [40,41]. A small and short phase 3 trial was done, giving the agent during radiotherapy and comparing responses to bethanecol treatment against artificial saliva, and found a significantly higher basal salivary rate with the active agent [42]. Further trials of sufficient size and with adequate controls are necessary to confirm that bethanecol has utility in either pre- or post-radiotherapy subjects, as well as in individuals with other etiologies of xerostomia.

Side effects with bethanecol were mild and related to the muscarinic agonist activity. General contraindications to use of bethanecol have been established for its currently urological indications, and include: hyperthyroidism, peptic ulcer, latent or active bronchial asthma, pronounced bradycardia or hypotension, vasomotor instability, coronary artery disease, epilepsy and parkinsonism. Both dose and frequency of use have not been established for xerostomia treatment.

**Nizatidine**

Nizatidine is an H2 receptor antagonist with the ability to inhibit acetylcholinesterase, resulting in an increased availability of acetylcholine. A small controlled, open-label trial in subjects with SS demonstrated improvement in stimulated salivary output and complaints of dry mouth [43]. The medication was well-tolerated and there were no significant AEs recorded. Further, more definitive, trials are indicated.

**ACUPUNCTURE**

Acupuncture, in particular in electro-acupuncture, has been reported to increase release of neuropeptides into saliva, such as calcitonin gene-related peptide (CGRP), neuropeptide Y (NPY) and vasoactive intestinal peptide (VIP), compared to baseline [44]. Hwato 0.32 mm x 40 mm needles were inserted to Si3, Si6 (face), Li4 (hands) and St36 (legs) points bilaterally to 5-10 mm depth, followed by manipulation until the DeQi needle sensation was obtained (ache, feeling of heaviness, and the sensation of a current originating from the needle point). Superficial needling (sham acupuncture) was not used as a control. For electro-acupuncture, low-frequency current (2 Hz) was used to Si6 and Li4, connected to the electro-pulser bilaterally. The current was adjusted to 2-4 mA to produce a pulsing, painless sensation. The mechanism of action of acupuncture is not known, but sensory stimulation, placebo and nocebo effects might play roles, modulated by discussion, listening and nurturing during the acupuncture sessions.

A systematic review analyzed if patients with irradiation-induced hyposalivation/xerostomia gain objective relief or subjective benefit from acupuncture [45]. Out of 61 records screened, only three were selected for qualitative synthesis: two of intermediate and one of poor quality, with a moderate (2) or high risk (1) of bias. The limited evidence suggested that acupuncture is beneficial for this indication, but was insufficient to recommend it.

In alternative medicine, comparison against the standard treatment is often lacking: its benefits, adverse effects and health economics should be related to standard treatments, e.g. saliva substitutes and mechanical (paraffin chew), chemical (pilocarpine, cevimeline) or electrical (Saliwell GenNarino®) stimulation of salivary responses.

**ELECTROSTIMULATION**

Human experiments showed that the application of an electrical current on the skin covering the parotid gland area and on the oral mucosa augmented salivary secretion [46,47]. A recent development is a device aimed at stimulating salivation by the application of electrical excitation in the area of the lower third molar (‘wisdom tooth’). The electrodes located on the surface of the device contact the oral mucosal surface which is 1-5 mm away from the lingual nerve. The rationale of the therapeutic potential lays with the stimulation imparted to the efferent trigeminal fibres running through the lingual nerve, which subsequently drive the submandibular and sublingual glands to secrete more saliva. However, reflex salivation by all salivary glands can be potentially evoked, as well, if the current excites the afferent fibres that relay to the superior salivary nucleus through the chorda tympani and the VII cranial nerve. The outcome is overall increased secretion by all salivary glands.

The current version of the device, called Saliwell GenNarino®, is a custom-made mouth-guard embedding an electronic circuit and a battery (Fig. 1). It is worn for a period of a few minutes, every time the patients feels need to increase the amount of saliva in the mouth. It is switched on and off by an infra-red remote control acting on a receiver, that is part of the electronic circuit. Therefore, double-blind testing is simple as the same device can be prompted by two identically looking but differently programmed remote controls to either be activated or to stay turned off.

The device was tested in a double-blind, sham-controlled study on 23 xerostomia patients, in which the use of the device during 10 minutes was shown to increase oral moisture, as measured by a wetness sensor placed on the appliance [48]. In a further multinational trial involving a mixed sample of 114 xerostomia patients, the device was evaluated during two months in a double-blind fashion. The activated device was superior to the sham in improving patient reported xerostomia severity and frequency and swallowing difficulties (Table 1) [49]. In an uncontrolled extension stage of this study, the positive effects remained after 11 months of use. At the end of the trial, other subjective parameters (oral discomfort, speech), frequency of awakening at night and salivary flow rate (both, unstimulated and mastication-stimulated) were better than at baseline [50].

No significant systemic AEs were observed. Some patients reported discomfort or irritation initially in the mucosal area in contact with the electrodes. Shortening of the electrodes solved the problem immediately. However, the manufacturer recommends caution and medical consultation prior to the device’s use in patients wearing a pacemaker, those who are pregnant or suffering from psychiatric or psychological disturbances.

**BIOLOGICAL THERAPY**

The primary drug of the current biological agents being used in the treatment of SS-induced hyposalivation is CD20-targeting ri-
Vanishing of primary saliva, by uptake of NaCl and secretion of Ca²⁺, Pi, with flow-rate > 0.10 ml/min (disclosed in a subgroup the stimulated whole saliva (SWS) flow-rate improved maximally active drug compared to baseline was achieved at week 12, when mastine, followed by oral prednisone for 5 days. Somewhat surpris-

After initial, open-label trials, a RCT treated 20 subjects with primary SS (pSS) with rituximab compared to 10 treated with pla-

Recognizing that the exocrinopathy of SS is driven by an auto-

Due to the difficulty in managing hyposalivation successfully, a large variety of treatment strategies have been attempted over the years. This section presents only a few examples of the approaches that are currently in experimental phase.

A number of studies have examined the efficacy of very low dose interferon α (IFN-α), 150 or 450 IU given orally, in SS. An initial, six month, single-blinded study showed significant increases in salivary output in the IFN group compared to control at each monthly examination [63]. This was followed by a 12 week phase II RCT. Although no changes were found in the primary endpoint of symptomatic oral dryness and unstimulated whole saliva, a sec-

Hypnosis has been suggested to be of some benefit in improv-

Human salivary gland excretory ducts possess c-Kit+ cells cap-

CONCLUSIONS

This manuscript has reviewed a variety of therapeutic ap-

chewing gums) and procedures that are not medical products (acupuncture). Therefore, those have been studied generally in uncontrolled and/or small-scale trials. On the other end, medications (pilocarpine, cevimeline) and medical devices (electrostimulator) are subject to stringent level of evidence in order to obtain marketing permission, and therefore, have generally been investigated in controlled and larger clinical trials.

The ultimate proof of efficacy of the different approaches is the degree of symptomatic improvement reached for every user, regardless of the patient characteristics (e.g. underlying diagnosis, severity of hyposalivation) [9]. There are very few patient-centered features that may guide the clinician in selecting the specific method to be used. One of those is the general health status of the patient. In some circumstances, the use of systemic sialogogues may be contraindicated. In these cases, any of the other applicable methods or agents may be selected.

In theory, the agents that stimulate salivary glands can only be of benefit for subjects with residual salivary gland function. According to this assumption, individuals with absolutely no salivary secretory capacity can only seek relief using salivary substitutes. However, it is almost impossible to ascertain that the entire salivary gland parenchyma has been destroyed by a cellular infiltrate (in SS) or radiotherapy. Even in extreme cases of oral dryness, residual activity may exist in minor salivary glands, but be undetectable by the clinician. Thus, use of stimulating agents (e.g. sialogogues, acupuncture, electrostimulation) may be of benefit in these cases, as their potential of increasing secretion, even to only a small extent, may alleviate the feeling of oral dryness [72].

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None declared.

CONFLICT OF INTEREST
Andy Wolff owns stocks of Saliwell Ltd., the manufacturing company of the electrostimulating device Saliwell GenNarino.
Management of Hyposalivation


