Salivary Enhancement Therapies

Philip C. Fox

Department of Oral Medicine, Carolinas Medical Center, Charlotte, N.C., USA

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Saliva · Secretagogues · Xerostomia · Caries · Sjögren’s syndrome · Radiotherapy

Abstract
When salivary output is reduced chronically to a significant extent, there is a marked increase in dental caries. As the role of saliva in protection of the oral hard tissue is well recognized, there have long been efforts to enhance salivary function in conditions with associated secretory hypofunction. The rationale is that by stimulating salivary output, caries and other oral complications will be reduced or eliminated. The most widely used method for increasing salivary function is a combination of masticatory and gustatory stimulation. A large number of systemic agents have also been proposed as secretagogues, but only a few have shown consistent salivary enhancing properties in well-designed, controlled trials. Pilocarpine has been shown to improve symptoms of oral dryness and to increase salivary output in patients with Sjögren’s syndrome and postradiation xerostomia. Recently, cevimeline has shown significant salivary enhancement in Sjögren’s syndrome. Pilocarpine and cevimeline have a similar mechanism of action, side effect profile and duration of activity. No secretagogues have been linked directly in clinical trials to either caries prevention or a reduction in the existing caries rate of salivary dysfunction patients. Improved secretagogues are needed, with fewer side effects, increased duration of activity and greater potency. Future research directions include gene therapeutic approaches to direct salivary growth and differentiation or modify remaining tissues to promote secretion, creation of a biocompatible artificial salivary gland and salivary transplantation. With improved secretagogues, the effects of conditions that result in reduced salivary function and increased caries will be ameliorated.

Saliva is a major protective factor in the oral cavity, providing protection for oral hard and soft tissues and support for critical oral functions [Mandel, 1989]. Salivary gland performance may be affected by a number of conditions. Reductions in saliva output and symptoms of oral dryness are a result of many systemic diseases, medical interventions and hundreds of pharmaceuticals [Fox et al., 1985]. When salivary function is compromised, there is a significant increase in oral complications. Prominent among these is a marked increase in dental caries. The loss of the antimicrobial, buffering, remineralizing and cleansing properties of saliva when secretory output is reduced may lead to rapid and severe caries. Other complications of salivary hypofunction include an increase in oral infections (particularly fungal species), mucosal pain and friability, difficulties with chewing, swallowing and speaking as well as prominent complaints of oral dryness (xerostomia).
Table 1. Salivary enhancement therapies

<table>
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<tr>
<th>Local/topical secretagogues</th>
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<tr>
<td>Gustatory stimulation</td>
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<td>Masticatory stimulation</td>
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<td>Oral rinses, gels, mouthwashes, artificial saliva</td>
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<td>Anhydrous crystalline maltose</td>
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<td>Acupuncture</td>
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<th>Systemic secretagogues</th>
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<tr>
<td>Pilocarpine HCl</td>
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<td>Cevimeline HCl</td>
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<td>Interferon α</td>
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<td>Bromhexine</td>
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<tr>
<td>Anethole trithione</td>
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<td>Traditional Asian mixtures</td>
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<td>Essential fatty acids</td>
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In an effort to address these complications in individuals who have reduced secretory function and complaints of dryness, many approaches have been proposed to enhance salivary output [Fox, 1997]. The rationale is that by providing greater quantities of saliva and its natural protective factors, caries and other oral complications will be reduced or eliminated. While this is a logical assumption, there is actually little proof from clinical research. Salivary function can be enhanced significantly, in a transient manner, but there is an absence of research in humans demonstrating a concomitant reduction in dental caries or other oral complications associated with salivary hypofunction. The problem is not one of negative studies, but of a lack of any studies of secretagogues which have used caries as an outcome variable. In general, clinical trials of salivary enhancement therapies have utilized improvement in oral dryness complaints as the primary outcome measure. Secondary outcome variables are usually measures of symptomatic changes in oral functions, such as speaking and swallowing, or other oral symptoms. Clinical trials of secretagogues have not measured parameters such as caries. This is likely due to the relative ease with which xerostomia and other subjective criteria can be monitored, compared to the lengthy and intensive processes necessary to quantify caries. Ideally, clinical trials should monitor subjective (symptomatic) and objective improvement from treatments designed to enhance salivary output.

Salivary enhancement therapies may be divided into local or topical approaches and systemic therapies (Table 1). While there have been many agents and techniques proposed for this purpose [Grisius, 2001], the following discussion will be restricted to those interventions that have controlled clinical trials for review. Although even this group is large, there are few interventions that have been studied in an adequate number of subjects in well-designed and appropriately controlled trials [Brennan et al., 2002].

Topical and Local Therapies

It is recognized that saliva output can be stimulated by oral activity. Chewing will result in a robust increase in saliva output. Salivation is also responsive to taste, particularly sour and bitter. The use of flavored gums and lozenges will increase secretory output and remains a mainstay of palliative therapy of xerostomia. The combination of gustatory and masticatory stimulation can transiently increase salivation and relieve symptoms of oral dryness. Patients with diminished salivation may be instructed to use sugar-free gums, lozenges, candies or mints for symptomatic relief of xerostomia. The use of sugar-free products must be stressed, as otherwise the addition of sugar bathing the dentition will only increase the caries risk and negate the benefit of increased salivary output.

Although not strictly a ‘local’ therapy, acupuncture relies on application of the needles to specific locations, often in close proximity to the oral cavity. There have been a number of clinical studies of acupuncture to treat xerostomia associated with Sjögren’s syndrome, radiotherapy or nonspecific causes [Blom et al., 1992, 1996; List et al., 1998; Blom and Lundeberg, 2000]. Results have been generally favorable, with the authors reporting some benefit for relief of symptoms and improvement in salivary output. It is mainly stimulated salivary function which has been positively affected by the therapy. One problem with these studies is the difficulty in providing appropriate placebo controls in clinical trials. An attempt at using superficial, non-site-specific acupuncture as a control found that the control group had similar improvements as the active acupuncture group. Other difficulties include a small sample size in the studies, a lack of double-blinding and the subjective nature of the reporting.

Recent research has attempted to define a mechanism by which acupuncture might affect salivary function. One group has identified at least two neuropeptides (vasoactive intestinal peptide and calcitonin gene-related peptide) which are increased in saliva following acupuncture...
treatments [Dawidson et al., 1998, 1999]. Since these can stimulate salivary function, it is possible that generation of increased amounts of neuropeptides could be responsible for any increase in salivation found. At present, acupuncture remains a possible approach to enhancing salivary function that requires further study. As one of the studies notes, acupuncture may serve as a ‘useful adjunct’ to management of the dry-mouth patient.

A very large number of agents – e.g. artificial salivas, oral rinses and gels, flavored mouthwashes – have been proposed to treat dry mouth. All these topical therapies likely provide some degree of transient salivary stimulation. There are few well-designed and controlled clinical trials that have tested these in a formal manner. It appears that different palliative treatments are favored by patients primarily based on personal preference. There is the suggestion that mucin-containing products may meet with better patient acceptance [Gravenmade and Vissink, 1993].

Recent clinical trials have reported on the use of a lozenge composed of anhydrous crystalline maltose as a treatment for dry mouth in Sjögren’s syndrome. In uncontrolled studies, salivary function increased and dry-mouth complaints decreased over 24 weeks of treatment. Due to the design of the trial, it was shown that this benefit was not the result of direct gustatory or masticatory stimulation [Fox et al., 2001, 2002].

**Systemic Therapies**

There are many systemic agents that are capable of stimulating salivary output (table 1). The drug with the most extensive clinical evidence is pilocarpine HCl.

**Pilocarpine**

Pilocarpine is a parasympathomimetic agent with mild β-adrenergic stimulating properties. It has been proposed as a treatment for dry mouth for over 100 years. A number of well-designed and well-controlled studies of substantial size have examined the affects of pilocarpine on dry mouth and salivary function in patients with Sjögren’s syndrome and postradiation salivary gland hypofunction [Fox et al., 1991; Johnson et al., 1993; LeVeque et al., 1993; Vivino et al., 1999; Horiot et al., 2000]. These clinical trials have consistently demonstrated that at doses of 5–10 mg 3 or 4 times daily, pilocarpine can significantly improve symptoms of dry mouth and increase salivary output.

Serious adverse events are rare with pilocarpine. While side effects such as sweating, flushing and urinary frequency are common, they are typically of mild or moderate intensity and of relatively short duration [Wiseman and Faulds, 1995]. Use of pilocarpine is contraindicated in patients with uncontrolled asthma, narrow-angle glaucoma or acute iritis. Caution is advised with use in patients with cardiovascular disease.

Clinical trials have utilized symptoms of dry mouth as the primary outcome variable. Secondary variables included salivary output, other oral dryness symptoms and the patient’s perceptions of oral functioning. Salivary secretion is maximally stimulated approximately 1 h after dosing with pilocarpine, and increases over baseline salivary output are found for 3–4 h [Wiseman and Faulds, 1995]. No tolerance to the secretagogue effects of pilocarpine has been reported, nor has long-term improvement in baseline salivary function been found. Increased salivary output is transient, dose-related and consistent [Bell et al., 1999].

Caries or changes in oral flora have not been studied in pilocarpine trials. There is a need for longer-term human trials with pilocarpine which measure caries or cariogenic bacteria, in order to demonstrate that improvement in xerostomia and an increase in saliva lead to a reduction in caries. There are some animal data supporting this, but further studies are needed [Bowen et al., 1988].

**Cevimeline**

Another parasympathomimetic agent, cevimeline HCl, has also been studied in large, well-controlled trials. At doses of 30 mg 3 times daily, cevimeline was shown to significantly improve symptoms of dry mouth and increase salivary output in patients with Sjögren’s syndrome [Petrone et al., 2002]. Cevimeline has a similar pharmacological profile to pilocarpine, although the onset of increased salivation may be somewhat later and the duration of action longer. The safety and adverse event profiles are very similar to pilocarpine as well, with sweating and nausea common complaints among patients. Cevimeline has been reported to have a high selective affinity for M3 subtype muscarinic receptors, the predominant receptor subtype in the salivary glands. This drug is currently being evaluated in clinical trials for use in postradiation xerostomia.

**Bromhexine**

Bromhexine has been proposed as a saliva enhancement therapy. However, there are no well-controlled studies which demonstrate that this agent will increase sali-
vary output or improve dry-mouth symptoms [Frost-Larsen et al., 1978; Manthorpe et al., 1981; Prause et al., 1984]. There may be some benefit for dry-eye symptoms in Sjögren’s syndrome [Tapper-Jones et al., 1980], but this has not been shown for the oral cavity.

**Anethole Trithione**

This agent has been demonstrated to increase salivation in individuals with mild dysfunction. Doses studied were 25 mg 3 times daily [Hamada et al., 1999]. In more severe cases of secretory hypofunction in Sjögren’s syndrome patients, anethole trithione was ineffective [Schiodt et al., 1986]. There was an interesting report suggesting a synergistic effect between anethole trithione and pilocarpine [Epstein and Schubert, 1987]. The mechanisms responsible for salivary stimulation may relate to upregulation of substance P and α-calcitonin gene-related peptide by the drug [Nagano and Takeyama, 2001]. There are inadequate clinical trials of this agent.

**Yohimbine**

There are limited studies for dry-mouth therapy with this α2-receptor antagonist. In a trial of dry mouth induced by antidepressants, significant secretagogue properties were found [Bagheri et al., 1997]. Further controlled clinical trials of sufficient size need to be conducted.

**Interferon α**

A number of large clinical trials have been reported using interferon α (IFN-α), as a high-dose injectable or a low-dose lozenge, for treatment of dry mouth and decreased salivation in Sjögren’s syndrome [Ferraccioli et al., 1996]. The injectable IFN-α is a recombinant protein, while the lozenge is a natural (cell line-derived) IFN-α. The low-dose lozenge formulation, at 150 IU 3 times a day, has been shown to reduce xerostomia and increase salivary output [Ship et al., 1999]. In one study in Sjögren’s syndrome patients, this preparation also improved minor salivary gland histopathology, reducing inflammatory infiltration and increasing normal-appearing acini, after 6 months of treatment [Shiozawa et al., 1998]. In a recent, large, well-controlled trial, unstimulated salivary function was reported to be significantly increased after 24 weeks of therapy with 150 IU lozenges 3 times daily, although complaints of oral dryness were not significantly improved [Cummins et al., 2003]. Side effects and adverse events were minimal. Further clinical trials will be necessary to define appropriate doses and to demonstrate fully the efficacy of this agent.

**Essential Fatty Acids**

Evening primrose oil and γ-linolenic acid have been investigated as a treatment for the dry mouth and eyes of Sjögren’s syndrome [Manthorpe et al., 1984]. While some improvements have been noted in ocular parameters, in a controlled trial, there was no significant benefit found versus a placebo control for oral or ocular signs and symptoms [Oxholm et al., 1986].

**LongoVital®**

LongoVital® is a herbal-based preparation with added vitamins. In a randomized, crossover trial of 40 Sjögren’s syndrome patients lasting 8 months, improvement was reported in salivary function during and following active treatment [Pedersen et al., 1999]. Certain inflammatory markers were also affected. A difficulty with this study is that it is unknown which of the multiple constituents of the preparation may be having an effect. As this is a single study, further clinical trials in larger numbers of subjects will be necessary before the efficacy of this agent is proven.

**Infliximab**

This biological agent is a tumor necrosis factor α blocker used in the treatment of rheumatoid arthritis. In preliminary studies in Sjögren’s syndrome, infliximab has shown significant benefit in a number of clinical and functional parameters, including increased salivary flow rate and improvement in symptoms of oral dryness [Steinfeld et al., 2001, 2002]. These results need to be replicated in larger studies. There is also concern about the risk of lymphoma with use of these agents, particularly in a condition such as Sjögren’s syndrome, where there is an underlying increased risk of this complication.

**Future Directions for Saliva-Enhancing Therapies**

There is a need for improved secretagogues that will have fewer side effects, an increased duration of activity and greater potency. Current therapies are restricted to agents which act primarily via the muscarinic receptor. Future drugs may be directed to other receptors on salivary cells. It is also possible that small-molecule drugs may be developed which target salivary receptors with greater specificity and consequently fewer adverse effects. Research should be directed towards targeting specific salivary glands and altering salivary composition to increase oral defenses. With better understanding of the
mechanisms of cell damage in systemic diseases such as Sjögren’s syndrome or following radiation therapy, new therapies will be devised directed at correction of underlying pathologies. These will likely have a beneficial effect on the salivary dysfunction accompanying these conditions.

Novel approaches will have to be found for individuals with too little remaining salivary function to be helped by salivary-enhancing therapies. In these individuals, directed salivary cell growth and repair may be possible, perhaps using gene therapeutic techniques. This will be feasible with improved knowledge of cell growth control. The goal would be natural repair of the salivary gland. There is also the possibility of salivary transplantation or use of a biocompatible artificial salivary gland. It is likely that a combination of these approaches will result in many more therapeutic options in the near future.

References


