Muscarinic Agonists in the Treatment of Sjögren's Syndrome

A Literature Review of Pilocarpine and Cevimeline

Assignment for the integrated master study in odontology

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Abstract

Sjögren's syndrome (SS) is a systemic autoimmune disorder that mainly affects the salivary and lacrimal glands, giving rise to clinical symptom such as oral and ocular dryness, xerostomia and keratoconjunctivitis sicca, respectively. When the disease occurs alone it is termed primary SS, and when in association with a connective tissue disease it is termed secondary SS. As of today, SS remains a benign, but non-curable disease. Treatment is mainly palliative. With better understanding of the disease pathogenesis, SS may be diagnosed at an earlier stage and targeted, interceptive treatment applied. SS may have multiple implications on oral health, and quality of life. Ocular manifestations are managed with local stimulation of the lacrimal glands, and supportive surgical procedures. Treatment of xerostomia includes strict oral hygiene regimes, saliva substitutes, and various agents to stimulate salivary flow. In this master thesis, we review the literature on the use of the muscarinic cholinergic agonists pilocarpine and cevimeline, which both have been shown to reduce symptoms of oral and ocular dryness in patients with SS.

Norwegian summary

Sjögrens syndrom (SS) er en systemisk autoimmun sykdom som primært påvirker spytt- og tårekjertler og gir kliniske symptom som tørrhet i munn (xerostomia) og øyne (keratokonjunctivitis sicca). Sykdommen forekommer enten alene å kalles da primær SS, eller sammen med en annen bindevevssykdom og kalles da sekundær SS. Per i dag finnes det ingen kur for å stanse utviklingen av SS, og behandlingen retter seg fremst mot å dempe symptomer. Ved bedre forståelse av sykdomsutviklingen kan sykdommen diagnostiseres tidligere, og målrettet forebyggende behandling tillempes. SS har flere konsekvenser for oral helse, og livskvalitet. Øye manifestasjoner behandles med lokal stimulering av tårekjertlene, og kirurgiske inngrep. Behandling av xerostomia inkluderer god oral hygiene, bruk av saliv erstatning, og stimulering av salivsekresjon på forskjellige måter. Denne prosjektoppgaven omhandler bruk av muscarine cholinerg agonistene pilocarpin og cevimelin, som begge har vist å kunne bedre symptom på munn- og øyetørrhet hos pasienter med SS.

Introduction

Sjögren's syndrome (SS) is an autoimmune, chronic inflammatory disease characterized by progressive focal mononuclear cell infiltration of exocrine glands, primarily the lacrimal and salivary glands. The lymphoid infiltrations are associated with clinical symptoms such as dryness of the mouth (xerostomia) and eyes (keratokonjunctivits sicca). Dryness of the nose, throat, vagina and skin has also been described. The peak incidence of the disease is in the fourth and fifth decade of life, with a female: male ratio of 9:1 (1).

The disease is named after the Swedish ophthalmologist Henrik Sjögren (1899 -1986) who in his doctoral dissertation in 1933 reported the detailed clinical and histopathological findings of 19 women with xerostomia and keratoconjunctivitis sicca, of whom 13 had chronic arthritis (2).

SS may occur as an isolated phenomenon with the clinical manifestations of xerostomia and keratokonjunctivits sicca, focal sialadenosis and/or serum auto antibodies. It is then termed primary Sjögren's syndrome (pSS). In cases where sicca symptoms occur in association with connective tissue disorders, the most frequent being rheumatoid arthritis (RA), systemic lupus erythematosus (SLE) or scleroderma, the disease is referred to as secondary Sjögren's syndrome (sSS) (1). Dry mouth and dry eyes are the most common subjective complaints of patients suffering from SS, and deviations in the quality and quantity of saliva may have a negative impact on dental and oral health. A predominant characteristic of patients with SS is reduced salivary flow rates of resting whole, and parotid saliva (3).

Increased incidence of cervical and root caries, oral candidiasis, mucositis (Table 1) and swelling of the salivary glands are frequent oral signs of SS. In addition to general discomfort, the lack of saliva may be accompanied by glossitis, angular cheilitis, problems in swallowing (dysphagia) and speaking, and alterations in taste (Table 1) (1, 4).

Table 1. Approximate frequency of oro-pharyngeal clinical manifestations in patients with Sjögren's syndrome. Adapted from Rhodus, 1999 (4).

Clinical manifestation	Prevalence %
Angular cheilitis	88
Glossitis	90
Mucositis	30
Glossodynia	45
Dysgeusia	75
Dysphagia	55
Candidiasis	83
Dental caries	100
Periodontitis	80

In comparison to other, more severe autoimmune diseases, symptoms of SS can seem minor. However, the complexity of symptoms and the chronicity of the disease will not only affect patient's quality of life but may also lead to significant morbidity and mortality owing to an increased risk of malignant transformation (5, 6).

Etiology and disease mechanisms of Sjögren's syndrome

SS is a complex disorder of unknown etiology. The susceptibility of disease can better be explained by an interplay between the environment and genetic factors (1), where an unknown environmental stimulus e.g., viral infections, may trigger SS in genetically predisposed individuals (Figure 1). Potential viral triggers includes Epstein-Barr virus (EBV), hepatitis C virus (HCV), and human T-cell leukemia virus (HTLV-1) (1). Albeit the level of genetic contribution is still far from being understood, findings in animal studies, candidate

gene association studies, and family aggregation studies confirm a genetic predisposition in the pathogenesis of SS (7).

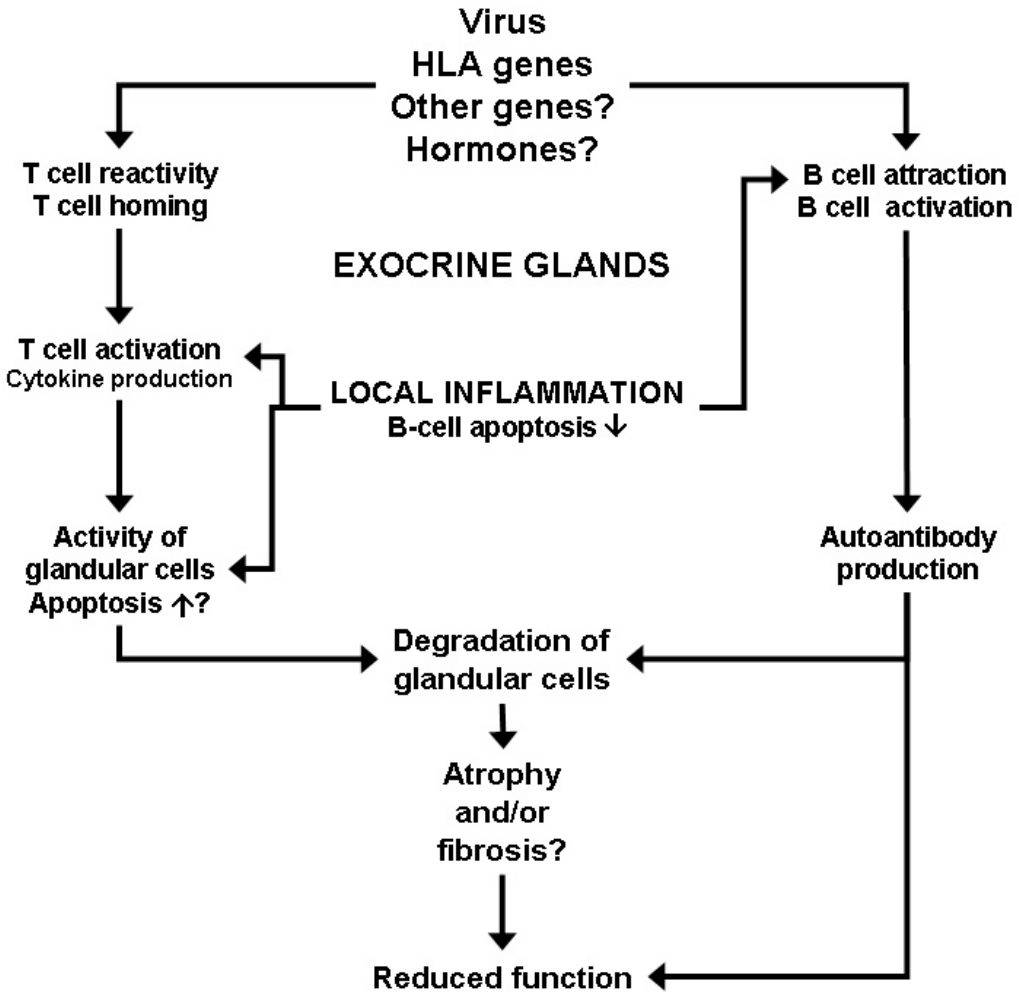

Figure 1. Possible events in the initiation and progression of disease in Sjögren's syndrome. Adapted from Jonsson et al 2005 (1).

In a very general way, the sicca symptoms in SS are attributed to lymphocytic infiltration of the glandular tissues, where the deficient secretory response of the salivary and lacrimal glands are thought to occur as a consequence of immune-cell mediated destruction of glandular tissues, eventually leading to the symptoms of dryness. However, processes

triggering lymphocyte recruitment into the exocrine glands, and the exact function of the cells while within the glands, are still a matter of speculation.

Recently**,** understanding of the pathology underlying glandular hypofunction has undergone a dramatic change. Firstly, many patients with SS have within their salivary glands large amounts of acinar tissue that is unable to function *in vivo.* Secondly, data from work on salivary acinar cells isolated from patients with SS demonstrates a reduced sensitivity to threshold levels of muscarinic stimulation, although the remaining tissue is functional *in vitro*. Overall, these findings suggest that the lack of glandular function in many patients with SS is the result of a perturbation of acinar function, ultimately followed by atrophy (8).

Diagnosis and management of Sjögren's syndrome

The diagnosis of SS should be based on several clinical and laboratory findings. The items classifying the oral component are based on the presence of subjective or objective oral dryness, and are usually considered cardinal features of SS. Over the years, different sets of classification criteria have been suggested for the diagnosis of SS. Among these are the Copenhagen criteria, the Californian criteria, the Greek criteria and the Japanese criteria (9). On the basis of latest data, a modified classification criteria (Table 2) set new rules for the correct classification of patients with pSS and sSS, and a list of exclusion criteria (Table 3) were drafted and approved by all the American-European Consensus group. Presently, the modified criteria most likely represent the best instrument available for the correct classification of SS.

Table 2. Revised American-European classification criteria for Sjögren's syndrome. Adapted from Vitali et al, 2002 (9).

I. Ocular symptoms (at least one of the following)

- Daily, persistent, troublesome dry eyes for more than 3 months.
- Recurrent sensation of sand or gravel in the eyes.
- Use of a tear substitute more than 3 times/day.

II. Oral symptoms (at least one of the following)

- Daily feeling of dry mouth for at least 3 months.
- Recurrent feeling of swollen salivary glands as an adult.
- Drinking liquids to help to wash down dry foods.

III. Objective evidence of dry eyes (at least one of the following)

- Schirmer's I test: 5 mm or below/5 minutes.
- Rose-Bengal score of 4 or greater according to the van Bijsterveld system.

IV. Histopathologic signs

- Minor salivary gland biopsy with focus score of 1 or greater.

V. Objective evidence of salivary gland involvement (at least one of the following)

- Salivary gland scintigrahy showing delayed uptake, reduced concentration and/or delayed excretion of tracer.
- Parotid scintigrahy showing the presence of diffuse sialectasias, without evidence of obstruction in the major ducts.
- Un-stimulated whole sialometry less than 1.5 ml/15 minutes.

VI. Laboratory abnormality (presence in the serum of the following auto antibodies)

- Antibodies to Ro/SSA or La/SSB antigens, or both.

Table 3. Revised rules for the classification of SS. Adapted from Vitali et al, 2002 (9).

For primary SS:

In patients without any potentially associated disease, primary SS may be defined as follows:

a. The presence of any 4 of the 6 items is indicative of primary SS, as long as either item IV (histopathology) or VI (serology) is positive

b. The presence of any 3 of the 4 objective criteria items (that is, items III, IV, V and VI)

c. The classification tree procedure is a valid alternative method for classification , although it should be more properly used in clinical-epidemiology survey

For secondary SS:

In patients with a potentially associated disease (for instance, another well defined connective tissue disease), the presence of item I or item II plus any 2 from among items III, IV and V, may be considered as indicative of secondary SS.

Exclusion criteria:

- Past head and neck radiation therapy
- Hepatitis C infection
- Acquired immunodeficiency syndrome
- Sarcoidosis
- Graft-versus-host disease
- Use of anticholinergic drugs (since a time shorter than 4-fold life of the drug)

Despite advances in the understanding of disease pathogenesis and clinical manifestations, physicians and dentist have long felt discouraged in the care of patients with SS. Current treatment of SS includes palliative treatment to manage dryness, stimulation of salivary gland function, treatment of systemic autoimmune features (Table 4), and management of non-specific symptoms such as fatigue (10). In the light of SS being an autoimmune disease, initial approaches were to treat the disease by immunomodulating drugs (Table 4) to alleviate the dry mouth and dry eyes symptoms. However, these drugs are usually reserved for severe cases of SS, involving extra-glandular manifestations or severe fatigue. Investigations looking solely into the treatment of dry mouth or eye symptoms using these agents are sparse (11, 12).

Table 4. Potential immunomodulating agents for the treatment of Sjögren's syndrome. Adapted from Mavragani et al, 2006 (3).

Agent	Formulation and dose	Outcome	Reference
Cyclosporine	5 mg/kg body weight daily	Improvement of subjective measures of xerostomia. No improvement of objective indices.	(3)
Methotrexate	0.2 mg/kg body weight weekly	Improvement in subjective measures. No improvement of objective indices.	(3)
Azathriopine	1 mg/kg body weight daily	No improvement detected. Adverse effects.	(3)
Corticosteroids	Systemic 0.5-1.0 mg/kg body weight daily	Limited evidence of improvement.	(3)
Hydroxychloroquinone	200 mg daily	No improvements in sicca symptoms.	(3)
Interferon-alpha	150 IU 3 times daily for 24 weeks (oromucosal route)	Improvement in oral and ocular symptoms, increase in un-stimulated whole salivary flow.	(13)
Nucleoside analogs	Zidovudine 250 mg twice daily	Significant improvement in sicca symptoms and objective measures.	(3)

Aims of the project

This study was undertaken with the general aim of reviewing the literature on the management of Sjögren's syndrome. The specific aims were to evaluate the therapeutic value of muscarinic agonists for the relief of symptoms of dry mouth, and to illustrate the clinical outcome of pilocarpine and cevimeline in stimulating salivary flow, as an effective long-term therapy for patients with SS.

Muscarinic receptors in Sjögren's syndrome

Acetylcholine (ACh) is a neurotransmitter mediating physiologic responses such as smooth muscle contraction, glandular secretion and cardiac rate, through a family of muscarinic acetylcholine receptors (mACR). The muscarinic receptor family is encoded by five muscarinic gene products designated M1 through M5 (14). In SS, the expression of mACR of the M1 and M3 subtypes in lacrimal and salivary glands is of particular interest (15). Interestingly, an increase in acinar cell expression of (M3R) muscarinic type 3 receptors has been demonstrated (16). Such an increase in M3R would be expected to result in acinar cell hyperfunction, a phenomenon that has been observed in the early stage of disease and in a very small number of patients (17). However, although the number of M3Rs in the salivary glands of patients with SS are increased, they were found to be hypo functional (14).

The understanding of the salivary gland dysfunction associated with SS, as well as the detection of antibodies that could precipitate muscarinic receptors with an antimuscarinic antibody activity has long been a matter of discussion. Recently, findings in non-obese diabetic (NOD) mice, an animal model of SS, could establish that M3Rs indeed are involved in the pathology responsible for salivary gland dysfunction (8).

In recent years, the development of sialologogues, i.e. an agent that stimulates salivary flow, have received interest for the treatment of SS (10). The use of muscarinic agonists such as pilocarpine or cevimeline which act through stimulation of M3 and M1 receptors, and its value as therapeutic option for the relief of dry mouth and dry eyes in patients with SS will be presented below.

Muscarinic agonist for treatment of Sjögren's syndrome

Pilocarpine

Pilocarpine is a natural tertiary alkaloid derived from the leaves of a bush in South America, called *Pilocarpus jaborandi* (Figure 2). The word jaborandi actually means "the slobber mouth plant", and Brazilian native Tupi Indians have for centuries known that chewing on the leaves of *Pilocarpus jaborandi* will stimulate salivary flow (12).

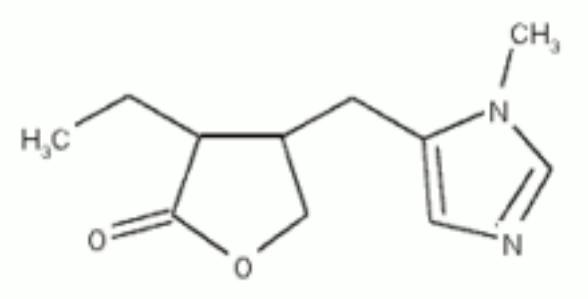

Figure 2. Chemical structure of pilocarpine. Adapted from Fox et al 2001 (14).

Absorption of pilocarpine from the gastrointestinal tract is rapid, and produces both a central and a peripheral muscarinic effect within 20 minutes of ingestion (14). Pilocarpine acts as a direct muscarinic agonist with activity at all muscarinic receptors (M1-M5). Metabolism mainly occurs in the liver, but approximately 20% is excreted unchanged in the urine, with an elimination half-life of approximately 0.76-1.3 hours (18).

Data from animal models suggest that regular use of pilocarpine may not only improve patient quality of life but potentially prevent complications such as caries and candidiasis. A study examined the effect of pilocarpine on caries using a model of partially desalivated rats (19). The animals' major salivary glands were surgically altered. They were then inoculated with

Streptococcus sobrinus, fed a diet that was over 50% sugar and allowed to drink water with 10% sugar. The group that had both submandibular and sublingual glands excised but were treated with pilocarpine, had a significantly reduced incidence of caries compared to partially desalivated, untreated controls, suggesting that at least in rats with dry mouth, administration of pilocarpine could be issued to prevent caries (19). These findings were confirmed in a second study where stimulation of saliva by pilocarpine treatment was able to reverse sucrose-induced fissure caries in albino rats (20).

In humans, pilocarpine has previously been used in ophthalmic preparations for the treatment of glaucoma, but the efficiency of pilocarpine in stimulating salivary flow as a long-term therapy for patients with primary and secondary SS has been confirmed in several studies, reviewed in (3, 21). Subjective and objective benefits of pilocarpine have also been shown in patients with radiation-induced xerostomia, a state similar to salivary changes in patients with SS (22).

Many studies have addressed the question of the optimal dosage of pilocarpine (Table 5). To investigate the efficacy and safety of pilocarpine, a prospective, randomized, double-blind, placebo-controlled trial was undertaken in 207 patients who received more than 40 Gy of radiation to the head and neck (23). The patients were given pilocarpine (5.0 mg or 10.0 mg orally three times a day) or placebo for 12 weeks, and were evaluated at baseline and every 4 weeks. In the patients receiving the 5 mg dose of pilocarpine oral dryness improved in 44 percent as compared with 25 percent of the patients receiving placebo. Overall improvement was achieved in 54 percent of the 5.0 mg group as compared with 25 percent of the placebo group, with a general increase in saliva production, as well as improved speaking, swallowing and chewing ability. Side effects were predominantly limited to sweating (23).

Most long-term studies report of doses 5.0 mg three times daily. Lower doses such as 2.5 mg three times daily did not seem to have an effect (18, 24), but neither did higher doses, such as 10.0 mg three times daily. Instead, higher doses were associated with more side effects, primarily increased sweating and drug intolerance (22, 23). Reports from a multicenter, placebo-controlled study in patients with SS indicated a significant increase in salivary secretion rate following pilocarpine administration, suggesting that the optimal dose of oral pilocarpine is 5.0 mg four times daily (25). Such as dosage was associated with marked clinical improvement and the lowest incidence of adverse effects (26).

Table 5. A summary of clinical studies evaluating the use of pilocarpine.

Etiology of xerostomia	Patients (n)	Controls (n)	Pilocarpine (dosage)	Outcome	Reference(s)
Diagnosis of SS (primary and secondary)	18	9	2% mg liquid ophthalmic drop preparation, 4 drops 3 times a day	Significant overall increase in parotid stimulated and whole un-stimulated salivary flow	(27)
Post-irradiation xerostomia in patients with head and neck cancer	207	5 mg (n=73) 10 mg (n=69)	5 mg tablets placebo or 10 mg pilocarpine 3 times a day	Improved saliva production and relieved symptoms of xerostomia	(23)
Radiation-induced xerostomia in patients with head and neck cancer	369	207	2.5 mg tablets first 4 weeks, 5.0 mg the next 4 weeks and 10 mg the last 4 weeks, three times a day	Significant clinical benefits; improvement in oral dryness, ability to speak, and mouth comfort	(22)
Diagnosis of SS (primary and secondary)	18	9	5.0 mg tablets single dose	Significant increase in labial salivary flow and whole salivary flow	(28)
SS	256	128	5.0 mg 4 times daily with escalation dose of 7.5 mg 4 times a day, 6 weeks after initiation of treatment	Significant relief of dry mouth symptoms at 20 mg/day, and ocular symptoms at 30 mg/day	(16)
Primary SS	60	46	5.0 mg in a 5% solution sublingually	Significant increase in stimulated salivary flow	(29)
Healthy subjects	40	10	10 ml. 0.5, 1 and 2% topical pilocarpine solution	Increase in salivary flow	(30, 31)
Xerostomia associated with radiotherapy, SS, sialadenosis, and xerogenic administration	45	-	5 mg tablets daily	Elevated salivary flow rate	(31)

To compare short-term effects of a single oral administration of 5.0 mg of pilocarpine on the salivary flow rate was measured in a mixed cohort study of 45 patients suffering from xerostomia due to radiotherapy, SS, sialadenosis, and medication. The best results were observed in the sialadenosis group followed by the patients with SS. The radiotherapy group experienced a slight increase in salivary secretion rate. Side effects were mild and did not affect compliance, highlighting the beneficial potential of the use of pilocarpine (22).

Long-term effects of pilocarpine were investigated in a single-blind, placebo-controlled study performed on 18 patients with SS. Nine patients received pilocarpine, and nine received placebo. Salivary stimulation was also compared between patients with pSS and sSS. In contrast to other studies, four drops of a liquid ophthalmic solution of 2% pilocarpine was applied orally three times a day for 6 weeks, the dosage being equivalent to previously described 5 mg 3 times a day. The results indicated a significant overall increase in both whole un-stimulated and parotid stimulated salivary flow in the pilocarpine group as compared with the placebo group. Two of nine patients experienced adverse effects, one being slight burning of the oral mucosa shortly after the initial administration of the drug, and the other a slightly increased diaphoresis. Concerning dosage, the results from this study support the therapeutic dose of 5.0 mg three times daily, suggesting pilocarpine as a safe, effective and available treatment for the stimulation of salivary flow in patients with SS (27).

A similar study investigated the salivary function in 60 patients with primary SS, by measuring un-stimulated basal salivary flow and stimulated salivary flow using a single dose of 5 mg of pilocarpine in a 5% liquid ophthalmic, administered sublingually. A significant increase in stimulated salivary flow was observed in comparison to anethole trithione (ANTT) stimulated salivary flow. Twenty-two of the 46 patients with low un-stimulated salivary flow had stimulation over 1.5 ml. Thus, pilocarpine even stimulated the residual function with an overall improvement in xerostomia perceived as better oral moisture and lubrication. In the

study, adverse appeared to be negligible; 2/46 (4%) patients experienced minor side effects, and respiratory or cardiovascular disease were not observed (29).

To determine whether treatment with pilocarpine tablets could alter chronic tongue and mouth burning symptoms related to oral candidiasis, twelve patients with this complication were investigated. Patients were given 5 mg pilocarpine tablets three times a day for twelve months. Salivary flow rates improved with the use of pilocarpine, and colony counts of *Candida albicans* were significantly reduced compared to baseline. The study concluded that in addition to using antifungal medications, a secretagogue may be useful for treatment of prevention of recurrent oral candidiasis and burning mouth syndrome in SS (32).

Due to different paths of progression in different patients and at different rates, the duration of symptoms as a predictor of response to therapy is insufficient. Histology is not always a useful predictor of response because neural dysfunction along with parenchymal damage also contributes to the pathogenesis of hyposalivation in SS. Salivary scintigrahy can also be used to determine the severity of glandular involvement, as well as the patients ability to form saliva (1).

Compared to other medications used in the treatment of SS (Table 4) pilocarpine can be considered a relatively safe drug with few severe side-effects. Adverse effects are primarily associated with the cholinergic activity of the drug and may include chills, dizziness, hyper salivation, flushing, increased lacrimation, sweating, heart palpitations, and gastrointestinal tract disturbance. Mild and tolerable side-effects are frequently reported during pilocarpine therapy, their incidence being dose-related. Sweating is reported as the most common adverse effect, reviewed in (12).

Pilocarpine is contraindicated in patients with uncontrolled asthma and obstructive pulmonary disease, as it may increase airway resistance, as well as muscle contraction and bronchial

secretion. Due to the possibility of cardiac disturbances, caution should also be applied in patients with cardiovascular disease and patients taking beta-adrenergic antagonists (24).

In general, it seems that the effects of pilocarpine treatment are restricted to ongoing therapy. If treatment is discontinued, symptoms will go back to baseline. Interestingly, both subjective and objective improvements are observed after some months of using pilocarpine, indicating that at least two to three months may be necessary to allow the medication to work (3, 26, 31). In cases where disease symptoms increase worse over time, it is suggested that it is the natural progression of the disease, not the pilocarpine losing effect (21).

Cevimeline

Originally described in the neuroscience literature as AF102B (Figure 3) cevimeline is a structurally rigid analog of acetylcholine that binds to muscarinic acetylcholine receptors with a relatively high specificity for muscarinic M1 and M3 receptors. Cevimeline shows a 40-fold greater relative affinity for the M3 receptor than for the M2 cardiac receptor compared with pilocarpine as well as long-lasting sialogogic action. In addition, the half- life of cevimeline in serum is longer than that of pilocarpine (15).

In preliminary studies on rodents and canines, administration of cevimeline significantly increased the volume of saliva excreted from the major salivary glands (33). Results from a double-blind, randomized, placebo-controlled study supported the therapeutic value of cevimeline for increasing lacrimal and salivary flow (34). A double-blind, randomized, placebo-controlled, multi-center trial enrolled seventy-five patients with SS and associated salivary gland dysfunction. Study participants were randomized to receive 30 mg or 60 mg of cevimeline or placebo, three times daily for six weeks. Regarding dosage, results supported

previous findings, where 30 mg of cevimeline three times daily seemed better tolerated and provided substantial relief of xerostomia as compared with the 60 mg therapy of cevimeline, which was associated with an increased occurrence in adverse effects, particularly gastrointestinal tract disorders (35).

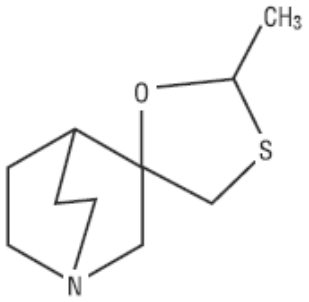

Figure 3. Chemical structure of cevimeline. Adapted from Fox et al 2001 (14).

Encouraged by success of early studies, the effects of cevimeline on various components in human saliva, such as immunoglobulin A (IgA), lysozyme and alpha amylase, were investigated in twelve patients with SS and fourteen healthy controls. The study demonstrated that cevimeline not only promoted salivary flow rate, but also increased the secretion of the previously mentioned salivary components. Thus, in order to prevent oral infections and other serious sequelae, the use of cevimeline may prove beneficial for patients with SS (36).

A recent study evaluated the effects of cevimeline on health-related quality of life and oral health status. The study was a randomized, double-blind, placebo-controlled crossover study. Patients received cevimeline 30 mg or matched placebo three times per day over 10 weeks, followed by a 4-week washout period, before treatment crossover. Patients were also asked to complete a set of questionnaires. Clinical assessments included sialometry, an intra-oral examination to determine the degree of xerostomia, hyposalivation-induced dental

complications. Results indicated a significant improvement in subjective xerostomia and general oral health following treatment with cevimeline. However, no improvement was observed in salivary flow rates or dry eye symptoms (37).

Table 6. A summary of clinical studies evaluating the use of cevimeline.

Etiology of xerostomia	Patients (n)	Controls (n)	Cevimeline (dosage)	Outcome	Reference
SS and associated salivary gland dysfunction	75	23	30 mg tablets 3 times daily, 60 mg 3 times daily or placebo	Cevimeline 30 mg 3 times daily gives substantial relief of xerostomia	(35)
SS patients with xerostomia and keratokonjunctivits sicca	197	70	Either placebo or 15 mg tablets 3 times a day or 30 mg 3 times a day	30 mg cevimeline 3 times a day gave substantive improvement in salivary and tear flow	(34)
SS (primary and secondary)	60	20	Either placebo or cevimeline 20 mg tablets 3 times a day or 30 mg 3 times a day	Statistically significant differences with 20 mg cevimeline	(38)
SS (primary and secondary)	12	14	30 mg capsule single dose	Promotion of salivary flow rate and increased secretion of salivary components	(36)
pSS (n=22) sSS (n=28)	50	23	30 mg tablet or placebo 3 times a day	General improvement in XI and GOHAI index	(37)

XI – xerostomia index; GOHAI – general oral health index

Conclusions

Salivary substitutes and oral moisturizers are the primary choices in initial, local treatment of xerostomia, but due to their minimal longevity and retentiveness, their effect is limited in patients with more than mild to moderate symptoms (10). Alternatively, saliva substitutes do not help, or are not tolerated (12). In these cases, pilocarpine and cevimeline may prove more effective in improving hyposalivation and xerostomia.

Pilocarpine has been approved in many countries including the USA and Sweden, but not in Norway. Nonetheless, in cases where pilocarpine is indicated, it may be ordered from Sweden under the registered name of Salagen® after applying for exemption from registration (39). In the United States cevimeline is registered under the name of Evoxac®, but due to lack of documentation proving safety and efficacy, the European drug authorities rejected the registration of cevimeline in 2001. Hence, to alleviate subjective and objective symptoms of xerostomia and hyposalivation in Scandinavian patients, pilocarpine will be the drug of choice for stimulating salivary flow.

Direct clinical comparisons in double-blind studies of pilocarpine and cevimeline in patients with SS are not yet available. However, data from pharmacological studies suggest that cevimeline has a longer plasma half-life than pilocarpine (14, 15). Moreover, a relative increase in specificity for binding to M3R and a decreased binding to M2 receptors, pilocarpine potentially gives more serious adverse effects due to cardiac tissue stimulation, in theory suggesting a benefit of cevimeline.

The recommended dosage of oral pilocarpine with minimal side effects is 5 mg four times a day (total 20 mg/day). However, an initial dosage of 2.5 to 5.0 mg three times daily (up to 30 mg/day) at variable dosage intervals may be considered for patients who have not responded

adequately with the 20 mg/day dosage. The management recommendation of cevimeline is 30 mg, given 3 times a day orally for the relief of hyposalivation and xerostomia in SS.

The primary endpoint for the therapeutic efficacy is increased salivary flow, which is not necessarily accompanied by symptomatic improvement. It may require up to 4 weeks for the peak effects of pilocarpine on salivary flow to be evident. Careful and frequent follow-up evaluations (6 to 8 weeks) are important to asses these parameters as well as to determine adverse effects and adjust dosage quantities and intervals. Pilocarpine may be administered indefinitely, as long as the salivary flow continues to be stimulated and the patient does not suffer severe side effects. Moreover, pilocarpine may be discontinued immediately and completely without adverse effects.

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