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Comparison of the effects of pilocarpine and cevimeline on salivary flow

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Abstract: *Objective:* The aim of the present study was to compare the effect of low-dose pilocarpine and cevimeline as stimulants for salivary flow in healthy subjects. *Methods:* In this cross-over clinical trial with a 1-week washout period, 40 male volunteers were submitted to an oral dose of pilocarpine 1% (Salagen^{TM}) –60 μg kg^{-1} body-weight (Group 1) or Cevimeline (Evoxac^{TM}) –30 mg (Group 2). Saliva samples were collected and the salivary flow rate was measured (ml min^{-1}) at baseline and 20, 40, 60, 80, 140 and 200 min after administration of drugs. In addition, salivary secretion was also measured under mechanical stimulation to observe salivary gland function. *Results:* The data were analyzed by Friedman and Wilcoxon signed-rank tests (significance level = 5%). Pilocarpine and cevimeline significantly increased salivary flow 140 min after intake. There was a significant higher secretion with cevimeline 140 and 200 min after administration. There were no differences seen among subjects in the salivary glands function by mechanical stimulation. *Conclusion:* Both drugs showed efficacy in increasing the salivary flow in healthy volunteers, but cevimeline was more effective than pilocarpine.

Key words: cevimeline; clinical trial; human subjects; pilocarpine; salivary flow

Introduction

Saliva is essential to maintain oral health by lubricating, cleaning and protecting the hard and soft tissues against bacteria, viruses and fungi. It is also important during speaking, tasting, masticating and swallowing, by maintaining oral and gastrointestinal mucus (1–3).

Xerostomia is a symptom associated with quantitative and qualitative changes in the salivary flow, which are generally attributed to salivary hypofunction. Several factors can cause a decrease in the salivary flow. These include autoimmune exocrinopathies (Sjögren's syndrome), anticholinergic effects of many drugs, tricyclic antidepressants, antihistaminic agents, antihypertensives and diuretics. Treatment of head and neck cancers with ionizing radiation, HIV infection, hepatitis C, Diabetes mellitus, hypertension, depression, aging, decrease of masticatory function, smoking, trauma, psychological and physiological changes can also negatively influence the salivary flow (4–9).

A significant reduction in the salivary flow usually interferes in the quality of life and can cause oral dysfunction, dental destruction, atrophy and ulceration of mucosa and mucosal infection. It is important to recognize and treat salivary flow dysfunction. The treatment of choice is usually some kind of sialogogue, with pilocarpine or cevimeline being the most used (2, 9–11).

Pilocarpine is an alkaloid imidazole obtained from the leaves of *Pilocarpus jaborandi,* and is a muscarinic–cholinergic agonist. The effect of this agent is because of the direct action on muscarinic receptors (M1 and M3) and it thus stimulates secretion by exocrine glands such as the salivary, sweat, lacrimal and respiratory mucous glands. Pilocarpine (Salagen^{TM}) is available in both tablet formulation (5 mg) and 1 and 2% solutions (12–19).

Cevimeline ((±)*cis*-2methylspiro[1,3-oxathiolane–5,3′-quinuclidine] mono-hydrochloride, hihydrate; SNI-2011; Evoxac^{TM} –30 mg capsules) is a quinuclidine analog of acetylcholine with a high affinity for M3 muscarinic receptors of both lacrimal and salivary glands. Previous studies have shown that muscarinic acetylcholine receptors found in human labial salivary glands are a mixture of the M1 and M3 subtypes, and that the M3 muscarinic receptor accounts for 93% of the precipitable receptors in parotid membranes. This drug has minimal adverse effects on other organs such as lungs and heart, which contain mainly M2 and M4 muscarinic receptors (7, 20–23).

The aim of the present study was to compare the ability of both pilocarpine and cevimeline to stimulate salivary flow of healthy volunteers.

Methods

Study population

Forty healthy male volunteers, aging 19–31 years (24.4 ± 2.3 years), weighing 62–108 kg (73.9 ± 9.5 kg) were enrolled in this single-blind, cross-over study. Exclusion criteria were: cardiac, hepatic, renal, pulmonary, neurological, gastrointestinal, hematological diseases and psychiatric disorders. Subjects were instructed to avoid any kind of drug therapy for at least 1 month prior to study and up to its completion. Volunteers were excluded if they were possibly sensitive to the medication of study or had used alcohol or cigarettes for a long period of time. This was performed to ensure that the existing degree of variation would not be because of the influence of illness or other medications. Volunteers were instructed to inform experimenters of any adverse events during the course of the study.

Drugs

Both pilocarpine 1% (Salagen^{TM}, MGI Pharma Inc., Bloomington, Minnesota, USA) and cevimeline (Evoxac^{TM}, Daiichi Sankyo, Inc., New York, New York, USA) were used in an individualized single-oral dose. The pilocarpine (solution) dose was adjusted to 60 μg kg^{-1} of body weight (maximum of 3.5 mg) and cevimeline was used as a single 30 mg-tablet.

The final doses according to the weight of each volunteer were 375.7 ± 57.0 μg kg^{-1} and 43.8 ± 6.7 μg of cevimeline and pilocarpine, respectively.

Clinical protocol

The study was conducted in a two-period cross-over with a 1 week washout period between treatments.

The study protocol was approved by the Ethical Committee of Sao Leopoldo Dental School, Campinas, SP, Brazil (# 05/185). All participants gave written consent after they were informed of the nature and details of the study.

After having fasted 1 h and 30 min prior to dosing, the subjects received a single oral dose of either pilocarpine 1% (Group 1) or cevimeline (Group 2), as previously randomized. After 1 week, the subjects of Group 1 received cevimeline and vice versa.

The salivary flow was quantified (sialometry) in ml min^{-1} by collecting all non-stimulated saliva during 5 min into sterilized graduated-tubes. The collection sialometries were carried out at zero (basal), 20, 40, 60, 80, 140 and 200 min after administration of drugs. All volunteers were submitted to a saliva collection with a mechanical stimulus by chewing 0.7 g silicone in a previous session to observe salivary gland function.

Statistical analysis

The statistical analysis was performed using BioEstat 4.0 for Windows® (Instituto de Desenvolvimento Sustentável

Maniraua, Belem, Para, Brasil, 2005). The effect of each drug over time was analyzed by Friedman test. The Wilcoxon signed-rank test was used to compare both drugs during each period. The significance level was set at 5%.

Results

All volunteers completed the study, no adverse effects were reported or observed and both drugs were well tolerated after the administration of a single oral dose.

The median (interquartile range) of stimulated saliva (baseline) showed no statistically significant differences ($P = 0.0916$) between Group 1 (1.4 ± 0.77 ml min^{-1}) and Group 2 (1.4 ± 0.85 ml min^{-1}).

The salivary flow before and after the administration of both drugs at different times is shown in Figs 1 and 2, respectively. Table 1 shows the comparison between medians of difference with basal salivary flow of each drug at each time point.

Figures 1 and 2 show that both pilocarpine and cevimeline significantly increased the salivary flow after 140 min. Both drugs almost doubled the salivary flow after 140 min, although cevimeline was higher than pilocarpine after 140 and 200 min (Table 1).

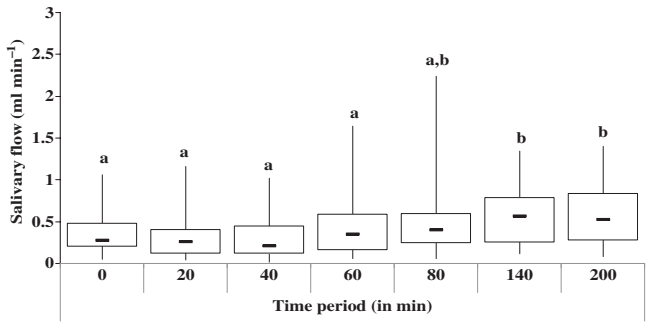

Fig. 1. Salivary flow (in ml min^{-1}) induced by pilocarpine (Group 1). Central line: median; Box: lower and upper quartiles; Whisker: maximum and minimum values.

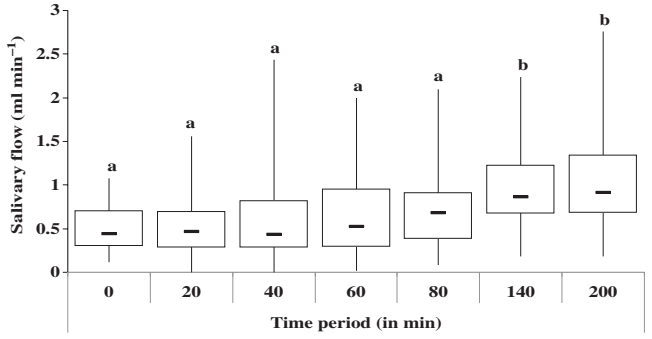

Fig. 2. Salivary flow (in ml min^{-1}) induced by cevimeline (Group 2). Central line: median; Box: lower and upper quartiles; Whisker: maximum and minimum values.

Table 1. **Mean (±SD) of differences with basal salivary-flow collected in the different times in relation of the two groups**

Time (min)	Group	Median of difference (±Interquartile deviation)	Interquartile range	*P* (Wilcoxon signed-rank test)
20	Pilocarpine	0 (±0.37)	−0.16/0.21	0.7061
	Cevimeline	0 (±0.21)	−0.09/0.12	
40	Pilocarpine	0 (±0.25)	−0.19/0.07	0.0925
	Cevimeline	0 (±0.29)	−0.11/0.18	
60	Pilocarpine	0 (±0.35)	−0.12/0.24	0.2675
	Cevimeline	0.13 (±0.37)	−0.04/0.33	
80	Pilocarpine	0.03 (±0.40)	−0.07/0.34	0.6001
	Cevimeline	0.16 (±0.50)	−0.01/0.49	
140	Pilocarpine	0.16 (±0.45)	0/0.45	**0.0013**
	Cevimeline	0.44 (±0.40)	0.29/0.68	
200	Pilocarpine	0.22 (±0.41)	0/0.41	**0.0023**
	Cevimeline	0.40 (±0.39)	0.3/0.69	

P values in bold represent statistically significant differences between drugs.

Discussion

Dry mouth or xerostomia induces several limitations regardless of the causes (secondary to autoimmune diseases, radiation and use of medications by young and elderly people). Usually, this condition is associated with other primary diseases or treatments, and the therapy for xerostomia must be safe and cannot interfere with the disease/treatment (4–9).

Both oral muscarinics (pilocarpine and cevimeline), acting on M3 receptors, have been approved by FDA (US Food and Drug Administration) and both increase salivary secretion. To our knowledge the present study is the first attempt to compare the effect on salivary secretion of both agents in healthy male volunteers. Female subjects were not included to avoid variation of salivary secretion during the menstrual cycle (24).

Pilocarpine is well known for its large parasympathetic stimulation, low toxicity and few side effects, when used at a low dosage. It increases the secretion of saliva only for a few hours and is useful to manage xerostomia secondary to radiation of the head and neck. It also has potential benefit for treatment of Sjögren's syndrome (12–19).

In the present study, the concentration of pilocarpine (60 μg kg^{-1}, orally administered) was able to induce a significant elevation of salivary flow after just 140 min. However, a numeric increase could be observed after 40 min. Duràn *et al.* (13) observed an increase in salivation after 15 min with a peak at 40 min after oral administration of pilocarpine (100–400 μg). A mouthwash of 2% pilocarpine solution showed a salivation peak

at approximately 45 min, keeping the salivary flow stable for at least 75 min (16). In the present study, the low pilocarpine concentration was probably responsible for the delay in the salivation peak. The low dose was chosen to reduce some of the typical adverse side effects, such as sweating, headache, nausea, mild abdominal pain, gastrointestinal upset, changes in urinary frequency, chills and influenza-like symptoms (rhinitis, flushing, increased lacrimation and palpitation). These adverse side effects are dose-dependent, (11) thus, in this study, the use of small doses provided a salivary flow increase and with minimal systemic manifestations is important clinically, as no adverse effects were noted by any volunteer.

Cevimeline has been frequently prescribed in the last few years, both in the USA and in Japan. It undergoes rapid metabolism and excretion, resulting in a relatively short half-life of approximately 50 min. The stimulating effect on saliva secretion usually lasts for about 6 h (7, 20–23). In the present research, it was more effective than pilocarpine in inducing salivation after 140 and 200 min. The probable reason is related with the pharmacokinetics of both drugs.

Pilocarpine is readily absorbed from gastrointestinal tract, reaching peak plasmatic-concentrations within 1 h, is metabolized by the liver, and excreted mainly by the kidneys. Its elimination half-life is approximately 1 h (2, 3, 7, 8, 11, 18). Cevimeline has the same profile regarding metabolization and excretion, but it has an elimination half-life of approximately 5 h. Both drugs, however, have the same adverse effects.

Cevimeline is a muscarinic agent that binds selectively to both M1 and M3 cholinergic receptors and pilocarpine is a nonselective muscarinic agent. These drugs' characteristics could have influenced the salivary flow differences observed in the present study. Generally, the usual dose of cevimeline recommended for chronic xerostomia is 30 mg t.i.d., as it is well tolerated and showing similar number/type of adverse effects in comparison with the placebo (7, 10, 11, 21–23). In this study, a single oral dose was used to compare it with the single dose of pilocarpine. It was able to improve salivary flow without signs of toxicity. Pilocarpine and cevimeline are safe and well tolerated, with no serious adverse effects, but chronic use (12 weeks or more) could be expected to produce side effects (diaphoresis, increased urinary frequency and facial flushing). Occasionally, other drugs have been used e.g. carbocholine, anethole trithone, pyridostigmine and bromhexine, but their mechanisms of action are largely unknown (7, 11, 16, 21).

Despite the use of healthy volunteers in the present study, data obtained from these subjects could be a good indicator of the effects expected of the studied drugs in dry mouth/xerostomic patients. The salivary flow rate can be altered by psychological factors, and the collection of saliva in a chairside fashion could influence the baseline salivary flow rate (7). However, the baseline salivary flow levels observed here were similar to the ones of previous studies that observed healthy volunteers and 3–5 times higher than the salivary flow observed in xerostomic patients (16, 20, 21).

Conclusion

The present study showed that both pilocarpine and cevimeline were able to increase the salivary flow in healthy volunteers, with cevimeline being more effective than pilocarpine. Additional studies are necessary to compare pilocarpine and cevimeline in xerostomic patients to corroborate the findings of the present study.

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