

Effect of pilocarpine mouthwash on salivary flow

R. Bernardi, C. Perin,
F.L. Becker, G.Z. Ramos,
G.Z. Gheno, L.R. Lopes,
M. Pires and H.M.T. Barros

Divisão de Farmacologia Básica e Clínica,
Departamento de Ciências Fisiológicas,
Fundação Faculdade Federal de Ciências Médicas
de Porto Alegre, Porto Alegre, RS, Brasil

Abstract

Pilocarpine is a cholinergic agonist that increases salivary flow and has been used to treat xerostomia. Oral intake is the most frequent route of administration. Adverse effects are dose-dependent and include sudoresis, facial blushing and increased urinary frequency. The objective of the present study was to evaluate the effects of topical pilocarpine solutions as mouthwashes on salivary flow and their adverse effects on healthy subjects. Forty volunteers received 10 ml 0.5, 1 and 2% pilocarpine solutions or 0.9% saline in a randomized, double-blind, placebo-controlled manner. Salivation was measured before and 45, 60 and 75 min after mouth rinsing for 1 min with 10 ml of saline or pilocarpine solutions. Vital signs were measured and ocular, gastrointestinal and cardiovascular symptoms, anxiety and flushing were estimated using visual analog scales. There was a dose-dependent increase in salivation. Salivation measured after 1 and 2% pilocarpine (1.4 ± 0.36 and 2.22 ± 0.42 g, respectively) was significantly ($P < 0.001$) higher than before (0.70 ± 0.15 and 0.64 ± 0.1 g), with a plateau between 45 and 75 min. Cardiovascular, visual, gastrointestinal and behavioral symptoms and signs were not changed by topical pilocarpine. Mouth rinsing with pilocarpine solutions at concentrations of 1 to 2% induced a significant objective and subjective dose-dependent increase in salivary flow, similar to the results reported by others studying the effect of oral 5 mg pilocarpine. The present study revealed the efficacy of pilocarpine mouthwash solutions in increasing salivary flow in healthy volunteers, with no adverse effects. Additional studies on patients with xerostomia are needed.

Key words

- Pilocarpine
- Mouth rinsing
- Mouthwash
- Xerostomia
- Salivation

Correspondence

H.M.T. Barros
Divisão de Farmacologia, FFCMPA
Rua Sarmento Leite, 245
90050-170 Porto Alegre, RS
Brasil
Fax: + 55-51-224-8822
E-mail: helenbar@ffcmpa.tche.br

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Introduction

Dry mouth or xerostomia is a common symptom most frequently associated with salivary gland hypofunction induced by transitory physiologic states, pathologic conditions or as a side effect of drug therapy or radiation (1-3). Xerostomia almost always develops after salivary gland destruction in

the course of treatment of head and neck cancers with ionizing radiation (4-6). Many autoimmune exocrinopathies such as Sjögren's syndrome present this symptom (7). On the other hand, the use of drugs like anticholinergics, tricyclic antidepressants, antihistamines, antihypertensives and diuretics can induce a marked reduction in salivary output (1,3,8-16). The aging process is an-

other factor that may induce salivary gland hypofunction because of chemical salivary changes, the use of medications or associated systemic diseases (10,17).

Chronic xerostomia compromises chewing, swallowing and speaking and predisposes to oral cavities and to a variety of destructive processes that include thinning, atrophy and ulceration of mucosa and fungal infections. All of these symptoms may be responsible for nutritional deficiencies and difficulties in communication and sleeping, leading to an overall decline in quality of life (2,5,7).

The treatment goals of patients with dry mouth are to relieve symptoms, to prevent or correct the consequences of salivary dysfunction, and to treat underlying disease (3). A number of treatments have been proposed to improve salivary function. Symptomatic treatments with saliva replacement (artificial saliva), hydration of oral mucosa with small sips of water, mastication or topical gustatory stimulation are largely palliative and generally offer only short-term benefits (6,18,19). Therefore, preventive therapies with fluoride, remineralizing solutions and antifungals may be necessary (3). Numerous systemic medications such as bromhexine, anetholetrithione and pilocarpine hydrochloride (3) have been tested as salivary stimulants. The most extensively studied sialogogue agent is pilocarpine (6).

Pilocarpine is a parasympathomimetic drug that exhibits potent muscarinic-stimulating properties. The pharmacological effects of this agent are multiple and include increase of smooth muscle tone and motility of the gastrointestinal and urinary tracts, gallbladder, biliary ducts and bronchi. An outstanding enhancement of salivary and sweating gland secretion is observed with pilocarpine (20) and these properties have been known in Western medicine for more than 100 years (20,21). Controlled studies to investigate the ability of pilocarpine to stimulate salivary flow and to relieve oral dryness

symptoms initiated in the 1960s. The results showed that pilocarpine is superior to placebo to relieve xerostomia complaints. At the present time it has been well established that oral pilocarpine is able to improve sicca symptoms, in particular those related to eyes and mouth in patients with systemic disorders such as Sjögren's syndrome (22-24) or other autoimmune conditions (25) and secondary to radiation therapy (26). After oral administration, the most common side effect is sweating, but urinary and gastrointestinal disturbances are also frequently reported (3,6,22). On the other hand, because pilocarpine is a parasympathomimetic drug, there is some risk of cardiovascular and pulmonary effects that make systemic administration somewhat dangerous. Patients with gastric ulcer and uncontrolled asthma should not use pilocarpine. Likewise, this drug must be used carefully by patients with controlled asthma, chronic bronchitis, pulmonary or cardiac disease, systemic hypertension, or using β -adrenergic blockers (6,7). Thus, a systematic approach to the study of the efficacy and potential side effects of topical pilocarpine administration used to enhance salivary flow is essential because of the possibility to use smaller dosages that could show a direct local effect with minimal systemic manifestations.

The purpose of the present study was to investigate the effect of pilocarpine solutions at different concentrations, applied by mouth rinsing, on salivary flow of healthy volunteers as well as to determine possible side effects secondary to this route of administration.

Subjects and Methods

The study was a placebo-controlled, double-blind, randomized clinical trial approved by the Research Ethics Committee. The sample was composed of 40 healthy volunteers, medical students from the Fundação Faculdade Federal de Ciências

Médicas, Porto Alegre, RS, Brazil, 18 to 30 years old, of both sexes (26 females and 14 males). Exclusion criteria were bronchial asthma, history of hypertension or hypotension, recent use of drugs, including smoking, suspected or confirmed pregnancy, heart, renal or hepatic diseases, peptic ulcer, hyperthyroidism, epilepsy, Parkinson's disease or parkinsonian syndrome, and HIV infection. Individuals who had experienced chemical or mechanical salivary stimulation (eating, drinking, smoking, oral hygiene, or chewing gum) within 90 min before the experiment were also excluded. To participate as volunteers all individuals signed a written informed consent term. After selection, the volunteers were randomly allocated to four groups, each consisting of 10 individuals homogeneously distributed by age and sex, in accordance with the solution to be used: 0.5, 1 or 2% pilocarpine or 0.9% saline.

Before the administration of solutions, each volunteer completed an analog scale (4) consisting of 11 elements to determine the intensity of symptoms of anxiety, tremor, sudoresis, facial flushing, abdominal and/or thoracic distress, lacrimation, salivation, palpitation, nausea, visual disturbances, and hunger. The individual could indicate a point on a 10-cm long line delimited by words expressing the highest and the lowest degree of each symptom. Blood pressure and heart rate were measured with a portable wrist blood pressure monitor (Omron, Vernon Hill, IL, USA). Salivary flow was quantified by weighing a piece of cotton (4 x 1 cm) that was kept under the tongue for 1 min. Salivary flow was measured before and 45, 60 and 75 min after mouth rinsing.

After the first salivary flow measurement, the volunteers were instructed to maintain 10 ml of the solution in the mouth for 1 min, without swallowing the solution and being very careful to spit the entire volume after this time. By the end of the 75-min period, blood pressure and heart rate were measured again, the volunteers were in-

structed to respond to the same analog scale used at the beginning of the experiment and were asked to estimate which solution had been assigned to them.

Statistical analysis was performed with the Sigma Stat 2.0 software (Jandel Scientific, Chicago, IL, USA) using a two-way repeated measures ANOVA for time and pilocarpine dose. Linear regression was used to establish the dose-response curve for pilocarpine solutions with respect to salivary flow. The replies to the analog scales were analyzed by one-way ANOVA. *Post hoc* dose comparisons were made by the Student-Newman-Keuls test. Multiple linear regression was used to verify the correlation between adverse effect parameters taken from analog scales and salivary flow. The Fisher exact test was used to compare the differences between treatment groups to correctly estimate the solution received. Statistical significance was defined as $P < 0.05$.

Results

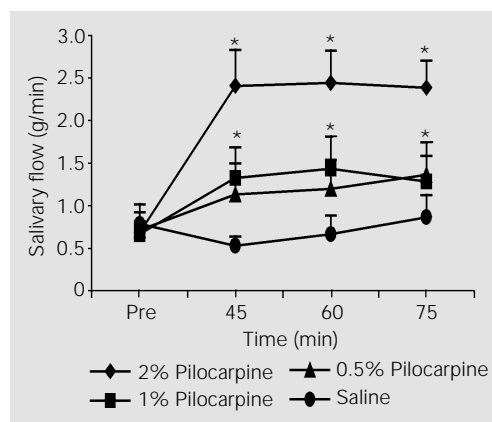
A *post hoc* comparison between groups indicated that mouth washing with 1 or 2% pilocarpine solutions significantly ($F = 4.803$, $P = 0.006$) increased salivary flow compared to saline solution. There was no significant difference in salivation at 45, 60 and 75 min after mouth rinsing with pilocarpine solutions ($F = 1.050$, $P = 0.382$). The increase in salivary flow induced by 1 and 2% pilocarpine was stable along the three moments of quantification, as illustrated in Figure 1. There was a dose-related increase in salivary flow (linear regression equation: $y = 0.601 + 0.818x$; $SE = 1.042$; $R = 0.512$).

The 2% pilocarpine solution was associated with increased sensation of salivary flow (sialorrhea), while the other pilocarpine concentrations and saline solution did not modify individual perception of salivation. All individuals who had received 2% pilocarpine or saline solution guessed correctly which solution had been administered. The

rates of correct answers to this same question were 80% for 1% pilocarpine and 50% for 0.5% pilocarpine.

No significant effects were observed in heart rate or blood pressure 90 min after administration of the pilocarpine solutions. Likewise, all other symptoms investigated did not differ significantly between groups (Table 1). However, the multiple linear regression test showed moderate but significant correlation ($R = 0.72$, $F_{5,34} = 7.338$) between the salivation parameter and symptoms of sialorrhea ($P = 0.04$), systolic pressure ($P = 0.005$), facial flushing ($P = 0.005$), thoracic distress ($P = 0.011$), and palpitations ($P = 0.020$).

Figure 1. Salivary flow (g/min) prior (Pre) to pilocarpine treatment and 45, 60 and 75 min after mouth washing with 10 ml of 0.5, 1 or 2% pilocarpine solutions or saline as the control solution for 1 min. * $P < 0.05$ compared to control (Student-Newman-Keuls test).



Discussion

Regardless of the causes of dry mouth or xerostomia (secondary to autoimmune disease, radiation, medications or aging) this condition induces several limitations to patients besides those produced by the primary disease. One has to keep in mind that these facts, combined with chronic diseases and/or treatments, make it necessary to search for a safe therapy of xerostomia.

Nowadays, 5 to 10 mg pilocarpine given by the oral route three or four times daily is considered to be safe and effective in stimulating salivary flow in patients with mild to severe secretory hypofunction (3). The mechanisms responsible for the effects of pilocarpine on salivary flow involve local and direct cellular stimulation (18). The parasympathetic action of pilocarpine induces water and electrolyte flow in saliva. There is evidence that pilocarpine also stimulates the production of mucin and of several other salivary constituents (4,19,27-29). Mucins are important to prevent infections and chemical or mechanical traumas to oral structures. Because mucin production occurs mostly in the small salivary glands, any increase in mucin will reduce xerostomia. Consequently,

Table 1. Estimation of adverse effects on healthy volunteers after mouth rinsing with pilocarpine solutions using visual analog scales.

Symptom	Saline	Pilocarpine (0.5%)	Pilocarpine (1%)	Pilocarpine (2%)	$F_{3,36}$
Sialorrhea	6.0 ± 0.65	5.7 ± 0.81	6.6 ± 0.63	8.9 ± 0.5*	4.803
Nervousness	1.9 ± 0.58	2.0 ± 0.84	3.3 ± 1.15	2.6 ± 0.71	0.574
Tremor	1.7 ± 0.66	1.6 ± 0.54	2.0 ± 0.86	2.5 ± 0.98	0.266
Sweating	1.7 ± 1.01	4.3 ± 1.29	4.9 ± 1.34	4.4 ± 1.32	1.326
Facial flushing	1.3 ± 0.36	2.9 ± 1.06	4.3 ± 1.31	2.5 ± 1.10	1.482
Abdominal distress	1.9 ± 1.04	2.8 ± 1.23	0.7 ± 0.39	1.7 ± 1.0	0.785
Lacrimation	0.8 ± 0.35	0.4 ± 0.51	0.7 ± 0.59	0.3 ± 0.21	0.749
Palpitations	1.7 ± 0.68	1.7 ± 0.71	0.9 ± 0.58	0.6 ± 0.26	0.906
Nausea	0.4 ± 0.16	1.3 ± 0.77	1.0 ± 0.68	0.8 ± 0.32	0.475
Thoracic distress	0.6 ± 0.34	0.4 ± 0.16	0.4 ± 0.16	0.5 ± 0.22	0.168
Blurred vision	0.4 ± 0.16	1.1 ± 0.58	2.3 ± 1.02	1.5 ± 0.99	1.049

Data are reported as means ± SEM. Bold represents significant F values (ANOVA = $P < 0.05$).

* $P < 0.05$ compared to control (Student-Newman-Keuls test).

even a small increase in salivary flow may induce symptomatic improvement for those patients who are treated with oral pilocarpine (3-5). On the other hand, several weeks must elapse before the symptomatic improvement becomes apparent because the reversal of the atrophic and desiccated changes induced by salivary deprivation does not occur immediately after pilocarpine (3-5). The long-term benefits of oral pilocarpine treatment against the consequences of xerostomia such as dental cavities or oral candidiasis, which are already experimentally demonstrated (15,30), require further studies in humans (6,31,32). There is no indication of the development of tolerance to the stimulant effect of pilocarpine on salivary flow (3,6).

In the present study, mouth rinsing with 1 and 2% pilocarpine solutions was able to induce a significant and dose-dependent elevation in salivary flow perceived subjectively and objectively, similar to what happens when pilocarpine is administered by the oral route (2,4,6,21,33,34). The latency to increase salivation when pilocarpine is administered by the oral route is 15 min, with a peak at 60 min and a duration of 2 or 3 h (2,6,27). Even though it is not possible to compare the latency of salivation after oral or topical pilocarpine administration it was clear that after topical administration the peak effect must have occurred earlier than 1 h and was stable for at least 75 min.

The adverse effects of pilocarpine are exaggerate responses of the autonomic nervous system. Some of these adverse effects

are frequently reported after chronic use of oral pilocarpine and are dose-dependent (4,5). Sudoresis (37 to 65%), increased urinary frequency (38%) and facial flushing (12 to 42%) are most likely to occur (4,6,18,27). Topical use of pilocarpine by mouth rinsing at the highest concentration used (2%) did not modify the blood pressure level or heart rate of healthy volunteers, comparable to when this drug is used orally (2,4,6,27). On the other hand, it was determined that facial flushing, palpitations and thoracic distress were positively correlated with the sialagogue effect. Since the linear regressions were significant, it is possible to infer that if excessive salivation is produced with higher pilocarpine doses than the ones used here, increased systolic pressure, facial flushing, thoracic distress and palpitations are the first adverse effects to be expected. In addition, the demonstration that salivary flow could be anticipated by the perception of increased salivation demonstrates a positive correlation between objective and subjective parameters. This finding also indicates that pilocarpine is effective in enhancing salivation and relieving xerostomia.

This clinical phase I study demonstrates that mouth washing with 10 ml 1 and 2% pilocarpine solutions increases salivary flow in healthy volunteers without inducing harmful adverse effects. More studies will be necessary to determine the efficacy of pilocarpine through this route of administration for treatment of xerostomic patients.

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