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ORIGINAL ARTICLE

Pilocarpine treatment in a mixed cohort of xerostomic patients

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OBJECTIVE: To compare the effect of a single 5-mg dose of pilocarpine hydrochloride on the salivary flow rate in three groups of xerostomic patients.

SUBJECTS AND METHODS: Forty-five patients were divided into three groups according to the etiology of their xerostomia: (i) radiotherapy; (ii) Sjögren's syndrome; and (iii) sialosis and xerogenic medications. Following the oral administration of a 5-mg pilocarpine hydrochloride tablet blood pressure, heart rate, body temperature and saliva secretion rates were monitored hourly for 3 h and adverse events were reported.

RESULTS: The most significant and persistent elevation of salivary flow rate was observed in the sialosis/drug-induced group followed by the Sjögren's syndrome group. The radiotherapy group presented a significant elevation of salivary secretion rate after 1 and 2 h, but returned to baseline at 3 h. No significant changes in vital signs were reported, except for low diastolic pressure measured at 1 h in the radiotherapy group. Several adverse events were recorded throughout the trial; however, only one patient withdrew from the study.

CONCLUSION: Treatment with pilocarpine hydrochloride tablets may improve saliva secretion in patients taking xerogenic medications and/or suffering from metabolic sialosis expanding the beneficial potential of this sialogogue.

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Keywords: pilocarpine; saliva; salivary glands; xerostomia

Introduction

Xerostomia affects more than 10% of the population (Field *et al*, 2001) with the proportion increasing in older adults (Sreebny and Valdini, 1988).

The causes of xerostomia can be classified as iatrogenic, immunogenic and metabolic. The most common iatrogenic source is xerogenic medications (Sreebny and Valdini, 1987; Scully, 2003). Less commonly radiotherapy (IR) for the treatment of head and neck cancer causes irreversible destruction of the parenchymal secretory gland tissue (Fox, 1998). Sjögren's syndrome (SjS), a chronic autoimmune disease, represents another group of xerostomic patients. SjS predominantly affects women and is characterized by the progressive destruction of the salivary gland tissue leading to xerostomia (Ship, 2002). In sialosis (sialadenosis) (SL), xerostomia is usually accompanied by a persistent painless bilateral swelling of the salivary glands, most commonly involving the parotids. Sialosis occurs in alcoholics, patients with diabetes and patients suffering from metabolic disorders, such as malnutrition and hyperlipidemia (Sheikh *et al*, 1996; Kim *et al*, 1998; Izumi *et al*, 2000).

Pilocarpine hydrochloride (HCl) was the first medication approved by the Federal Drug Administration for the treatment of salivary gland impairment induced by IR to head and neck cancer patients and for SjS patients. Few studies describe the use of pilocarpine for treating other conditions associated with xerostomia such as chronic graft-*vs*-host disease (Nagler and Nagler, 1999) and xerogenic medications (Mercadante *et al*, 2000; Götrick *et al*, 2004; Masters, 2005).

Here, we present a comparative study of 45 patients suffering from xerostomia due to IR, SjS, SL and xerogenic medications (MD) and their response to a single 5-mg dose of pilocarpine HCl.

Subjects and methods

Patient group

Forty-five patients with a primary complaint of dry mouth were evaluated at our Salivary Gland Clinic and divided into three groups (Table 1): (i) radiotherapy (eight patients treated with I^{131} radiotherapy for thyroid cancer and additional five patients exposed to external beam irradiation); (ii) SjS diagnosed according to the classification criteria for Sjögren's syndrome: American–European Consensus Group (Vitali *et al*, 2002); and (iii) SL/MD group. Patients were diagnosed as suffering from SL on the basis of clinical, serologic or

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Table 1 Patient characteristics

Group	*No. of patients (M/F)*	*Mean age ± s.d. [range]*
IR	13 (5/8)	52 ± 18 [24–84]
SjS	13 (1/12)	61 ± 11 [48–82]
SL/MD	19 (3/16)	57 ± 15 [23–78]

IR, radiotherapy induced; SjS, Sjögren's syndrome; SL/MD, sialosis/xerogenic medication.

sialographic imaging. Additionally, persistent painless bilateral enlargement of parotid glands for at least 3 months, accompanied by systemic diseases such as diabetes mellitus, hypertension, hypothyroidism and lipid disorders supported this diagnosis. The MD group consisted of patients taking xerogenic medications including analgesics, antidepressants or other psychoactive drugs, diuretics, antiacids, or antihypertensive agents. SL and MD patients were combined because many patients suffered from both disorders (Table 1).

Patients suffering from glaucoma, cardiac arrhythmias, pulmonary and bladder problems were excluded from the study.

Study protocol

The study was conducted between 8:00 hours and 12:00 hours, 2 h after eating, mouth wash usage or tooth brushing. Unstimulated whole salivary flow rate (UWSFR) and stimulated (with 2% citric acid applied to the lateral margins of the tongue) whole salivary flow rate (SWSFR) were collected by spitting for 10 min before (baseline) and 1, 2 and 3 h after 5-mg pilocarpine HCl was taken. Systolic and diastolic blood pressure, heart rate and body temperature were measured at each time point. All patient complaints were recorded during the entire study.

Statistical analysis

Distribution for categorical variables was analyzed using the chi-square test (large sample) and the Fisher–Irwin exact test (small sample). For continuous variables the ranges, mean values, standard deviations and standard errors were calculated as indicated. Comparisons between groups were analyzed with ANOVA. Paired observations were analyzed using *T*-test for paired differences. Correlations between pairs of variables were determined by Spearman correlation.

Results

Patients' profile

Mean age was not significantly different between the groups ($P = 0.70$) (Table 1).

Monitoring of blood pressure, pulse rate and body temperature

No significant changes of systolic blood pressure occurred relative to baseline in either group (Figure 1). Diastolic pressure was significantly lower in the IR group at the 1-h measurement compared to baseline

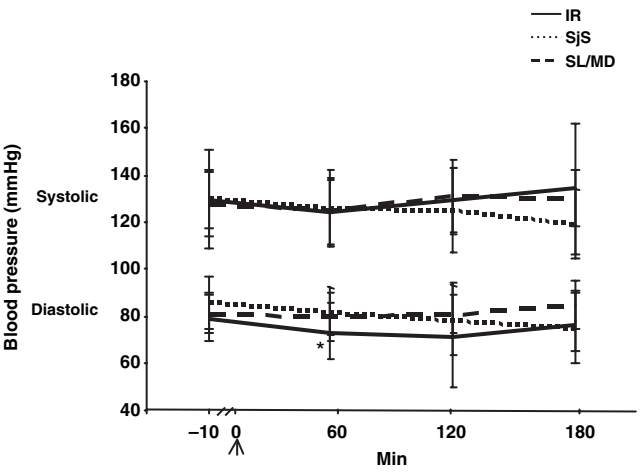

Figure 1 Blood pressure measurements; before and after pilocarpine HCl administration. IR; radiotherapy induced; SjS; Sjögren's syndrome; SL/MD; sialosis/xerogenic medication. Arrowhead; pilocarpine administration. $*P \leq 0.05$

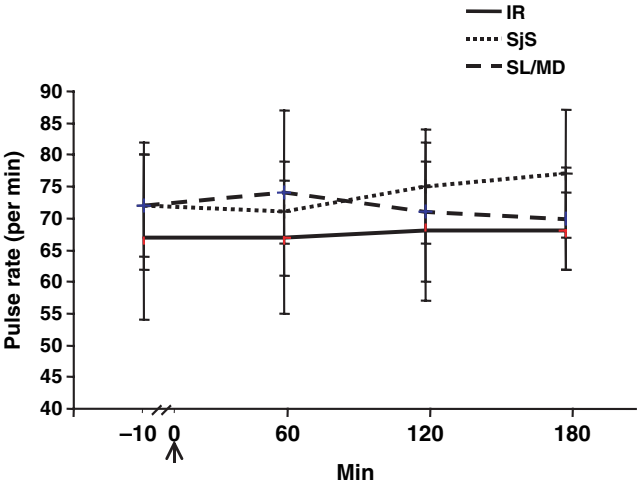

Figure 2 Pulse rate before and after pilocarpine HCl administration. IR; radiotherapy induced; SjS; Sjögren's syndrome; SL/MD; sialosis/xerogenic medication. Arrowhead; pilocarpine administration

($P = 0.012$) (Figure 1). This difference was not apparent at the 2-h ($P = 0.87$) and 3-h ($P = 0.62$) periods (Figure 1). None of the groups showed significant changes in pulse rate and body temperature at any time point (Figures 2 and 3).

Salivary secretion rate

The greatest effect of pilocarpine HCl on salivary secretion rate was observed in the SL/MD group with higher flow rates at the 3-h time point compared to baseline for both UWSFR and SWSFR (fourfold and twofold, respectively) (Figure 4) .

In the IR group a significant increase in UWSFR and SWSFR was observed, peaking at 1 h ($P = 0.01$ and 0.04, respectively) and gradually decreasing. At 2 h the flow was still significantly higher ($P = 0.013$ and 0.05, respectively), but both measures returned to basal levels at 3 h.

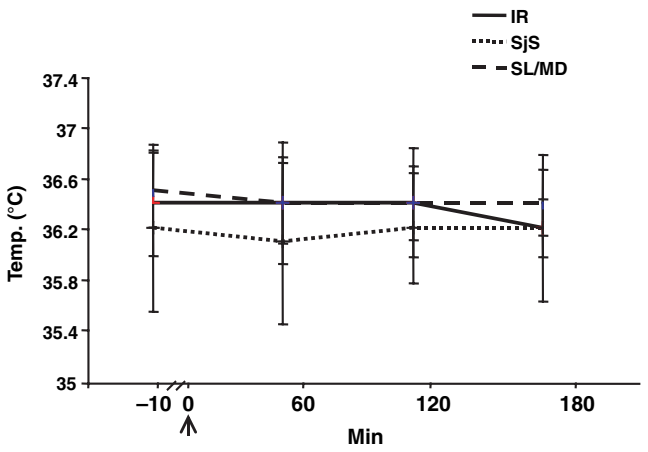

Figure 3 Body temperature before and after pilocarpine HCl administration. IR, irradiation induced; SjS, Sjögren's syndrome; SL/MD, sialosis/xerogenic medication. Arrowhead, pilocarpine administration

In the SjS group, significantly higher UWSFR was seen after 1 and 2 h ($P = 0.034$ and 0.036, respectively) almost returning to baseline levels after 3 h (Figure 4). Higher SWSFR were observed at the 2-h and 3-h time points ($P = 0.026$ and 0.001, respectively).

Adverse events

Thirty-three percent of the patients complained of one or more side effects during the study. The most common side effect was urinary frequency (28%) followed by dizziness (15%) and sweating (11%) (Table 2). Nevertheless, all except one patient with diabetes from the SL/MD group completed the study. There were no significant differences in the number of patients suffering from side effects between the three groups (IR 33%, SjS 54%, SL/MD 26%, $P = 0.32$). Most patients complained of one side effect, with no significant difference in number of complaints between the groups ($P = 0.54$) (Table 3).

Discussion

Xerostomic patients suffer from rampant dental caries, frequent mucosal infections, difficulties in chewing food and swallowing. Patients also become very sensitive to spicy food, suffering from altered taste sensation and perception as well as experiencing considerable pain originating from the salivary glands. Coughing episodes, voice disturbances, speech difficulties and discomfort are also present (Pedersen *et al*, 2002). Together these signs and symptoms significantly decrease patients' quality of life (Fox, 1998).

We present three groups of xerostomic patients with diverse etiologies underlying their salivary gland impairment. Radiotherapy including radioiodine therapy causes irreversible destruction of parenchymal and ductal tissue (Fox, 1998; Mandel and Mandel, 2003). SjS is an autoimmune disorder accompanied by a long-term destructive process due to lymphocytic infiltration to the secretory tissue (Ship, 2002).

The mechanisms underlying SL/MD-induced xerostonia are not fully understood. Changes in salivary gland parenchyma induced by metabolic disorders, interference with central pathways, blockade of muscarinic and/or adrenergic receptors in the glandular cells have been proposed (Sreebny and Schwartz, 1997). The

Table 2 Type and frequency of adverse effects according to patient group

	Group			
Complaint (%)	*IR*	*SjS*	*SL/MD*	*Total*
Urinary frequency	46	31	26	34
Dizziness	23	8	21	17
Sweating	8	8	21	12
Tremor	8	8	16	11
Flushing	15	8	11	11
Headache	8	8	16	11
Tremor	8	8	16	11
Nausea	8	8	–	6
Chest pressure	8	–	5	4
Sleepiness/tiredness	8	–	5	4
GI irritation	8	–	–	2
Rhinitis	–	8	–	2
Blurred vision	8	–	–	2
Weakness	–	–	5	2

GI, gastrointestinal; IR, radiotherapy induced; SjS, Sjögren's syndrome; SL/MD, sialosis/xerogenic medication.

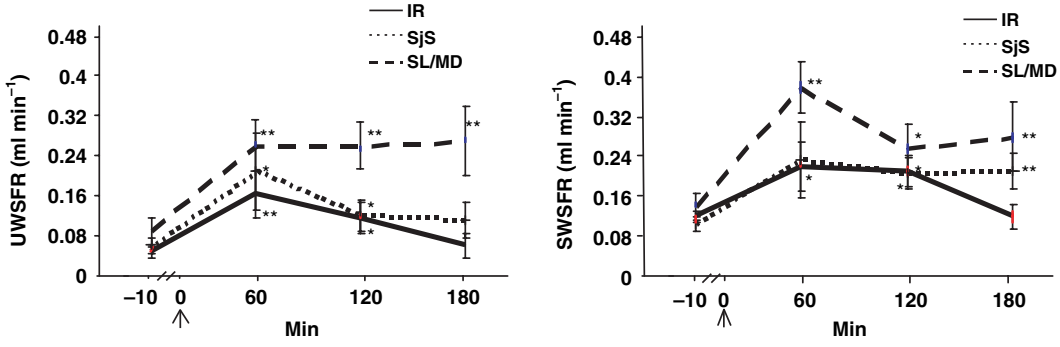

Figure 4 Saliva secretion rate before and after 5-mg pilocarpine HCl administration. USWSFR, unstimulated whole salivary flow rate; SWSFR, stimulated whole salivary flow rate; IR, radiotherapy induced; SjS, Sjögren's syndrome; SL/MD, sialosis/xerogenic medication. Arrowhead, pilocarpine administration. $*P \leq 0.05$; $**P \leq 0.01$

Table 3 Comparison of the number of complaints per group

No. of complaints	*IR (%)*	*SjS (%)*	*SL/MD (%)*
0	30	54	26
1	38	30	37
2	8	8	21
3	8	–	16
4	8	–	–
5	8	8	–

IR, radiotherapy induced; SjS, Sjögren's syndrome; SL/MD, sialosis/xerogenic medication; no significant differences were found ($P = 0.54$).

most common cause of dry mouth is drugs with more than 400 compounds known to have xerogenic side effects (Sreebny and Valdini, 1987). In some patients xerogenic medication can be changed, sparing them much discomfort. However, in many cases the beneficial role of the drug is more important than the mouth dryness, and no alternative medication is appropriate. Furthermore, many patients take more than one xerogenic medication increasing their effect on salivary gland impairment.

Pilocarpine HCl is a non-selective muscarinic agonist with a mild β-adrenergic ability. This parasympathomimetic agent enhances saliva secretion, ameliorating the sensation of dry mouth in patients with preserved exocrine tissue (Ship, 2002; Fox, 2004). Moreover, there is no evidence of tolerance to the salivary-stimulating properties of pilocarpine even after 5 months of consecutive treatment (Wiseman and Faulds, 1995).

The mean salivary flow rate can increase to twofold up to 10-fold upon pilocarpine administration (Wiseman and Faulds, 1995). In the present study, the most significant effect on salivary secretion was a threefold increase from baseline value after 3 h in the SL/MD group (Figure 3).

In the SjS group, a transient higher flow rate was observed in unstimulated secretion. Upon gustatory stimulation a higher steady state secretion was observed (Figure 4) suggesting retained functional ability of the secretory tissue.

A transient and modest elevation of secretion was found in the IR group, keeping with previously published data demonstrating that hyposalivation in patients following head and neck radiotherapy responds minimally to systemic sialgogues including pilocarpine (Gorsky *et al*, 2004).

In this study, baseline UWSFR measurements were 0.046, 0.06 and 0.09 ml min^{-1} (IR, SjS and SL/MD groups, respectively) lower than the accepted cut-off value (0.1 ml min^{-1}) between normal and abnormal UWSFR (Sreebny and Valdini, 1988). The only patients with significantly higher UWSFR and SWSF rates 3 h after taking pilocarpine were in the SD/MD group.

Few studies explored the benefits of pilocarpine as an adjuvant in the treatment of drug-induced xerostomia. Mercadante *et al*, 2000 described mild relief from xerostomia in opiod-treated cancer patients using pilocarpine. Moreover, the medication was well tolerated and no patients withdrew from the study (Mercadante *et al*, 2000). Pilocarpine has also been reported to improve constipation, urinary retention and sedation in a lung cancer patient treated with morphine (Mercadante, 1998).

Götrick *et al* explored the effect of pilocarpine use on opioid-induced oral dryness. They found significant increases in salivary flow and the only adverse effect experienced was elevated sweating in two individuals (Götrick *et al*, 2004). Masters (2005) reported the substantial relief of dry mouth in psychiatric inpatients taking psychoactive medications by using pilocarpine HCl. Salah and Cameron (1996) demonstrated the benefits of pilocarpine for anticholinergic adverse effects in a patient under desipramine treatment for major depressive disorder (Salah and Cameron, 1996).

The muscarinic receptors M1 and M3 are located in the salivary glands and are responsible for salivation. Since muscarinic receptors are located in other organs, adverse effects can be observed. For example, the M2 receptor is the most prominent receptor found in the heart and is responsible for the cardiac side effects of muscarinic agonists. With the exception of one case report using oral tablets of pilocarpine (Hendrickson *et al*, 2004), no serious reactions or toxicities have been reported in controlled trials applying the medication (Wiseman and Faulds, 1995).

In our study, one-third of the patients complained of side effects (Tables 2 and 3) with urinary frequency the primary adverse event followed by dizziness and sweating. The majority of the patients experienced either no adverse effects or only one (Tables 2 and 3). Previous reports also demonstrated sweating as the major adverse effect (33.5%) seen in patients treated with 5-mg pilocarpine HCl t.i.d. with urinary frequency as the second most common side effect (9.1%) (Hendrickson *et al*, 2004).

In this study, the administration of 5 mg of pilocarpine had no significant effects on vital signs including pulse rate, systolic blood pressure and body temperature (Figures 1–3). Similar to reports found in the literature, pilocarpine was well tolerated by all patients (Wiseman and Faulds, 1995; Fox, 2004).

Pilocarpine is contraindicated in patients with uncontrolled asthma, acute iritis or narrow-angle glaucoma. Caution is advised in patients with controlled asthma, chronic bronchitis, chronic obstructive pulmonary disease or cardiovascular disease as well as when co-administrated with β-adrenergic antagonists or drugs with parasympathomimetic or anticholinergic effects (Wiseman and Faulds, 1995). Although many patients taking antihypertensives and medications for cardiac diseases suffer from drug-induced xerostomia, pilocarpine should be prescribed with caution.

Based on the results of the present study, we recommend a trial using a single 5-mg dose of pilocarpine in these patients, with regular monitoring of vital signs and side effects before considering chronic use.

In conclusion, the current study investigated the short-term effects of administration of a single dose of 5 mg of pilocarpine HCl on salivary gland function in

three groups of xerostomic patients: IR, SjS and SD/MD. The most significant elevation in saliva flow was observed in the SD/MD group. Side effects were mild and did not affect compliance. These observations highlight a new venue in the treatment of the large (and expanding) xerostomic population.

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