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ORIGINAL ARTICLE

Pilocarpine for the treatment of salivary glands' impairment caused by radioiodine therapy for thyroid cancer

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OBJECTIVES: To study the effect of single-dose pilocarpine hydrochloride 5 mg on the whole unstimulated and stimulated salivary flow in patients suffering from thyroid cancer treated with radioiodine therapy, and to investigate the changes in vital signs during the treatment.
SUBJECTS AND METHODS: Five such patients were referred with complaints of dry mouth, rampant caries, and pain in the parotid gland region or history of chronic recurrent suppurative sialodenitis. A single dose of 5 mg pilocarpine hydrochloride was administered to each patient and blood pressure, heart rate, body temperature and salivary secretion rate were monitored at 1, 2 and 3 h.
RESULTS: A significant elevation of unstimulated and stimulated saliva flow rate was observed in four patients without significant alteration of the monitored vital signs.
CONCLUSIONS: Treatment with pilocarpine hydrochloride may be beneficial in the case of impaired salivary function in patients treated with radioiodine.
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Keywords: salivary glands; pilocarpine hydrochloride; xerostomia; radioiodine therapy; thyroid cancer

Introduction

Salivary glands are composed of highly differentiated epithelial cells and are capable of secreting, besides copious amounts of fluid, proteins with quite specialized intraoral functions (Baum, 1993). Saliva is essential for adequate function of the mouth such as lubrication, chewing and swallowing, facilitating speech, enhancing taste perception and cleansing action of the hard and soft tissues of the oral cavity. Saliva also contains digestive enzymes and plays an important role in soft tissue repair and maintenance of the ecological balance of oral microflora as well as helping the immunity and defense of the oral cavity (Pedersen *et al*, 2002).

Radioiodine therapy with ^{131}I for thyroid cancer patients causes salivary gland impairment manifested mainly by episodes of parotid sialadenitis (Mandel and Mandel, 2003). Temporary decrease of salivary flow develops immediately after radioiodine therapy followed in some cases by permanent xerostomia (Allweiss *et al*, 1984). The mechanism of injury is not well understood, being attributed to either direct damage by ^{131}I of the epithelial parenchyma of the parotid glands' intralobular ducts or indirectly, through hormonal and metabolic derangements (Markitziu *et al*, 1993; Mandel and Mandel, 2003).

Pilocarpine hydrochloride (HCl) is mainly a non-selective muscarinic agonist with mild β-adrenergic ability serving as parasympathomimetic agent to enhance salivary secretion and to reduce the feeling of dry mouth in patients with preserved exocrine tissue (Ship, 2002; Fox, 2004). Pilocarpine is the first medication approved by the federal drug administration for treating patients suffering from dry mouth caused by radiotherapy or Sjögren's syndrome. Severe events induced by pilocarpine are rare while the most common adverse effects include sweating, flushing and urinary frequency (Fox, 2004). Pilocarpine is contraindicated in patients with history of uncontrolled asthma, bronchospasm, severe chronic obstructive pulmonary disease, congestive heart disease, acute iritis and narrow-angle glaucoma. Caution is advised when used in patients with cardiovascular disease (Fox, 2004). After ingestion of the drug, salivary secretion reaches maximal stimulation at 1 h with high levels of salivary output found after 2 h (Wiseman and Faulds, 1995). Mean salivary flow rate can attain up to 10-fold higher values than after placebo (Wiseman and Faulds, 1995). No tolerance to pilocarpine has yet been reported (Fox, 2004).

Here we present five patients suffering from long-term salivary gland impairment after radioiodine therapy and their response to 5 mg pilocarpine HCl intake.

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Patients and methods

Five patients (2 men and 3 women; mean age 53 years; range, 39–72 years) complaining of dry mouth, rampant caries, and pain of the parotid gland region and recurrent episodes of parotid sialadenitis agreed to participate in this study (Table 1). All patients received radioiodine therapy at least 3 months prior to the study. The patients did not smoke and did not suffer from glaucoma, cardiac arrhythmias, pulmonary, bladder problems or an autoimmune disease.

Study protocol
The study was conducted between 8:00 and 12:00 AM, after 2 h free of food intake, mouth wash use or tooth brushing. Unstimulated and stimulated (2% citric acid) whole salivary flow was collected for 10 min before and at 1, 2 and 3 h after the ingestion of 5 mg pilocarpine HCl. Systolic and diastolic blood pressure, heart rate and body temperature were measured at each time point. Patient's complaints and subjective feelings were recorded during the study.

Statistical analysis
For continuous variables, ranges, medians, mean and standard errors were computed. The data were tabulated, analyzed and compared using Wilcoxon matched-pairs rank test (Wilcoxon, 1945) with alpha for significance set at 0.05. Data are presented as mean ± s.e.m.

Results

Patients' profile
Five patients previously treated with radioiodine (range 3–132 months, mean 34 months) for thyroid cancer and suffering from long-term salivary gland impairment were given one single dose of 5 mg pilocarpine HCl and were monitored for salivary secretion rate as well as vital signs and potential side effects (Table 1). ^{131}I therapeutic dose ranged between 5.55 GBq (150 mCi) and 20.35 GBq (550 mCi). A range of signs and symptoms suggesting salivary gland impairment were reported by the patients including dry mouth sensation, rampant dental caries, radiating pain from the parotid gland area during eating and chronic sialadenitis with recurrent swelling of the parotid glands. Assessment of salivary gland function was established with ^{99m}Tc-pertechnetate scintigraphy in all except one patient that demonstrated impairment of parotid gland function. Furthermore, in two patients with relative higher ^{131}I therapeutic dose the right submandibular gland was affected as well (Table 1).

Changes in blood pressure, pulse rate and body temperature
None of the patients had significant elevation in systolic or diastolic blood pressure in comparison with baseline measurements (Table 2). Heart rate and body temperature did not change significantly compared with base line measurements (Table 2).

Salivary secretion rate
All patients except patient no. 3 reported improvement of their subjective dry mouth sensation. Patient no. 1 experienced fatigue that resolved after an hour. All patients except patient no. 3 responded to pilocarpine HCl intake with increased unstimulated and stimulated whole salivary flow rate (UWSFR, WSFR respectively) (Table 3). Significant elevation was found after 120 min for UWSFR ($P = 0.05$) and after 60 and 120 min for WSFR ($P = 0.042$).

Discussion

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

Salivary glands are sensitive to radioactive iodine (^{131}I) therapy as they possess the capacity to concentrate and secrete iodine up to 100 times serum level (Mandel and Mandel, 2003). The main area for iodine transport in the salivary glands is the epithelium of the parotid intralobular ducts. Iodine is extracted from periductal capillaries and concentrated by the ductal epithelium. In the process of concentrating the radioactive iodine, the salivary parenchyma is directly exposed to irradiation. Moreover, ^{131}I also causes endothelial damage to glandular vasculature further enhancing injury to gland's secretory apparatus.

Early sialadenitis is the most frequent complication of ^{131}I therapy for thyroid cancer. Other early

Table 1 Patients characteristics

Patient	*Age*	*Gender*	*Total I^{131} (GBq)*	*Duration post I^{131} therapy (months)*	*Affected salivary glands by scintigraphy*	*Signs and symptoms*
1	39	F	20.35	132	LP + RP + RS	Dry Mouth
2	56	F	9.25	4	LP + RP + RS	Dry Mouth, rampant caries
3	72	M	5.55 + 40 Gy external radiation therapy	3	N.E.	Dry mouth
4	47	F	5.55	3	RP	Pain of RP area during eating
5	49	M	5.55	30	LP + RP	Bilateral chronic suppurative sialadenitis, dry mouth

N.E., not established; LP, left parotid; RP, right parotid; RS, right submandibular.

Table 2 Alterations of pulse rate, systolic and diastolic blood pressure and body temperature during the 3-h protocol

Time (min)	0	60	120	180
No. of patients	5	5	5	2
Pulse rate (min^{-1})				
Range, median	64–78, 70	68–80, 72	66–80, 72	64–70, 67
Mean ± s.e.m.	70.4 ± 2.92	73.6 ± 2.04	73.6 ± 2.48	67.0 ± 3.0
P-value		0.50	0.28	0.32
Systolic BP (mm)				
Range, median	120–145, 135	110–140, 130	130–140, 140	120–140, 130
Mean ± s.e.m.	135 ± 5	126 ± 7	136 ± 3	130 ± 10
P-value		0.27	0.58	0.32
Diastolic BP (mm)				
Range, median	80–90, 90	80–90, 90	80–90, 90	80–90, 85
Mean ± s.e.m.	87 ± 2	87 ± 2	87 ± 2	85 ± 5
P-value		1.00	1.00	0.32
Body temperature (°C)				
Range, median	36.2–37.1, 36.8	36.5–36.9, 36.6	36.3–36.8, 36.6	36.3–36.6, 36.45
Mean ± s.e.m.	36.7 ± 0.16	36.64 ± 0.07	36.56 ± 0.09	36.45 ± 0.15
P-value		0.57	0.58	0.65

Comparison of blood pressure, pulse rate and body temperature before and after pilocarpine HCl intake using Wilcoxon matched-pairs rank test.
*$P \leq 0.05$.

Table 3 Alterations of USWFR and SWSFR during the 3-h protocol

Time (min)	0	60	120	180
No. of patients	5	5	5	2
USWSFR (ml min^{-1})				
Range, median	0–0.21, 0.10	0–0.4, 0.30	0–0.4, 0.30	0.14–0.24, 0.19
Mean ± s.e.m.	0.107 ± 0.04	0.242 ± 0.08	0.252 ± 0.07	0.190 ± 0.05
P-value		0.17	0.05*	0.18
SWSFR (ml min^{-1})				
Range, median	0.075–0.4, 0.20	0.28–0.55, 0.50	0.25–0.61, 0.36	0.24–0.42, 0.33
Mean ± s.e.m.	0.215 ± 0.05	0.422 ± 0.06	0.384 ± 0.06	0.33 ± 0.09
P-value		0.042*	0.042*	0.18

Salivary secretion rate before and after 5 mg pilocarpine HCl ingestion.
USWSFR, unstimulated whole salivary flow rate; SWSFR, stimulated whole salivary flow rate.
*$P \leq 0.05$ using Wilcoxon matched-pairs rank test.

complications concerning the orofacial complex include mucositis and oral candidiasis (Bushnell *et al*, 1992; Mandel and Mandel, 2003), taste alteration and facial nerve palsy (Bushnell *et al*, 1992; Levenson *et al*, 1994). Occurrence of radioiodine induced salivary dysfunction is often delayed and tends to be permanent (Malpani *et al*, 1996). Late damage to the salivary glands leads to chronic sialadenitis, xerostomia, dysphagia, poor oral hygiene and loss of appetite (Mandel and Mandel, 2003). As opposed to ionizing irradiation with external beam, ^{131}I therapy usually does not completely destroy gland ability to secrete saliva preserving adequately functional parenchyma to respond upon stimulus. Moreover, it is well-known that preserved functional parenchymal tissue can compensate by producing higher amount of saliva (Eisbruch *et al*, 1999). As differentiated thyroid cancer has a good prognosis, reduction of long-term oro-facial side effects of radioiodine therapy is essential in maintaining patient's quality of life.

Radiation effects are more frequently reported following radioiodine doses >14.8 GBq (400 mCi) (Malpani *et al*, 1996). In our study, a dose of 5.5 GBq had a long-term effect on the salivary glands as demonstrated by scintigraphy and sialometry (Tables 1–3).

The 'cut-off' value between normal and abnormal unstimulated whole salivary secretion rate was suggested to be 0.1 ml min^{-1} (Sreebny and Valdini, 1988). Others suggested hyposalivation cut-off between 0.16 and 0.2 ml min^{-1} (Navazesh *et al*, 1992). In this study basic salivary rate was 0.107 ± 0.04 ml min^{-1} with a twofold increase upon stimulation (Table 3) suggesting xerostomia but still with residual functional parenchyma.

Previously, pilocarpine was given during the radioiodine therapy in order to promote the discharge of iodine from the glands and to reduce the absorbed dose by a reduction of the effective half-time and a non-significant trend of reduced side effects was observed (Alexander *et al*, 1998).

Our study showed that a single dose of pilocarpine HCl 5 mg induced a significantly increased unstimulated and stimulated salivary flow rate (Table 3). The non-responding patient (no. 3) received in addition to ^{131}I therapy, 40 Gy of external beam radiation therapy to the head and the neck region including the submandibular glands in the radiation field.

A recent study by Gorsky *et al* (2004), suggested that hyposalivation in head and neck irradiated patients may have minimal response to systemic sialgogues including pilocarpine. It is well established that if therapeutic external radiation treatment to the head and neck area exceeds ~50 Gy, irreversible damage to the salivary glands glandular epithelium occurs (Taylor and Miller,

1999). Indeed, studies suggested that a mean dose of 26 Gy should be the planning goal if substantial sparing of salivary glands in the radiation field is desired (Eisbruch *et al*, 1999). We assume that in patient no. 3, the additive damage by the iodine therapy and the external beam on the salivary resulted in total absence of minimal secretion ability and therefore no capability to enhance secretion by gustatory and pharmacological stimulation.

Interestingly, additive secretion response of pilocarpine to citric acid stimulation was observed (Table 3). Sour taste, produced in our study by citric acid, has the highest potential for stimulating salivary flow compared with other tastes (Pedersen *et al*, 2002).

Nevertheless, in a recent study (Nakada *et al*, 2005), lemon candy abuse in close temporal proximity to ^{131}I administration resulted in enhancement of side effects on subsequent salivary gland function. The authors postulated that as blood flow to salivary glands is improved by sucking lemon candy, a greater amount of ^{131}I may be delivered to the salivary gland resulting in more damage to the secretory parenchyma (Nakada *et al*, 2005). In our study the use of gustatory reflex was established at least 3 months after radioiodine therapy was completed resulting in beneficial response (Table 3).

No significant effect regarding pulse rate, blood pressure alterations as well as body temperature was observed during the study (Table 2). Moreover, no severe side effects were reported by the patients. Consequently, treatment with pilocarpine HCl in the short run is safe and well tolerated in this category of patients.

Long-term treatment with pilocarpine HCl in patients suffering from salivary gland impairment may further reduce the severity of signs and symptoms.

In conclusion, the current study investigated the effect of short-term usage of pilocarpine HCl treatment on salivary gland impairment in radioiodine treated patients with thyroid cancer. Pilocarpine administration produced short-term increase in salivary output accompanied with negligible side effects.

These findings open a new avenue for the treatment of oro-facial morbidity. A larger scale of investigation is needed to confirm the benefits of this strategy for the long-term maintenance of patients' quality of life.

References

Alexander C, Bader JB, Schaefer A, Finke C, Kirsch CM (1998). Intermediate and long-term side effects of high-dose radioiodine therapy for thyroid carcinoma. *J Nucl Med* **39:** 1551–1554.

Allweiss P, Braunstein GD, Katz A, Waxman A (1984). Sialadenitis following I-131 therapy for thyroid carcinoma: concise communication. *J Nucl Med* **25:** 755–758.

Baum BJ (1993). Principles of saliva secretion. *Ann N Y Acad Sci* **694:** 17–23.

Bushnell DL, Boles MA, Kaufman GE, Wadas MA, Barnes WE (1992). Complications, sequela and dosimetry of iodine-131 therapy for thyroid carcinoma. *J Nucl Med* **33:** 2214–2221.

Eisbruch A, Ten Haken RK, Kim HM, Marsh H, Ship JA (1999). Dose, volume, and function relationships in parotid salivary glands following conformal and intensity-modulated irradiation of head and neck cancer. *Int J Radiat Oncol Biol Phys* **45:** 577–587.

Fox PC (1998). Acquired salivary dysfunction. Drugs and radiation. *Ann N Y Acad Sci* **842:** 132–137.

Fox PC (2004). Salivary enhancement therapies. *Caries Res* **38:** 241–246.

Gorsky M, Epstein JB, Parry J, Epstein MS, Le ND, Silverman S Jr (2004). The efficacy of pilocarpine and bethanechol upon saliva production in cancer patients with hyposalivation following radiation therapy. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* **97:** 190–195.

Levenson D, Gulec S, Sonenberg M, Lai E, Goldsmith SJ, Larson SM (1994). Peripheral facial nerve palsy after high-dose radioiodine therapy in patients with papillary thyroid carcinoma. *Ann Intern Med* **120:** 576–578.

Malpani BL, Samuel AM, Ray S (1996). Quantification of salivary gland function in thyroid cancer patients treated with radioiodine. *Int J Radiat Oncol Biol Phys* **35:** 535–540.

Mandel SJ, Mandel L. (2003). Radioactive iodine and the salivary glands. *Thyroid* **13:** 265–271.

Markitziu A, Lustmann J, Uzieli B, Krausz Y, Chisin R. (1993). Salivary and lacrimal gland involvement in a patient who had undergone a thyroidectomy and was treated with radioiodine for thyroid cancer. *Oral Surg Oral Med Oral Pathol* **75:** 318–322.

Nakada K, Ishibashi T, Takei T *et al*. (2005). Does lemon candy decrease salivary gland damage after radioiodine therapy for thyroid cancer? *J Nucl Med* **46:** 261–266.

Navazesh M, Christensen C, Brightman V. (1992). Clinical criteria for the diagnosis of salivary gland hypofunction. *J Dent Res* **71:** 1363–1369.

Pedersen AM, Bardow A, Jensen SB, Nauntofte B. (2002). Saliva and gastrointestinal functions of taste, mastication, swallowing and digestion. *Oral Dis* **8:** 117–129.

Ship JA. (2002). Diagnosing, managing, and preventing salivary gland disorders. *Oral Dis* **8:** 77–89.

Sreebny LM, Valdini A. (1988). Xerostomia. Part I: Relationship to other oral symptoms and salivary gland hypofunction. *Oral Surg Oral Med Oral Pathol* **66:** 451–458.

Taylor SE, Miller EG. (1999). Preemptive pharmacologic intervention in radiation-induced salivary dysfunction. *Proc Soc Exp Biol Med* **221:** 14–26.

Wilcoxon F. (1945). Individual comparisons by ranking methods. *Biometrics* **1:** 80–83.

Wiseman LR, Faulds D. (1995). Oral pilocarpine: a review of its pharmacological properties and clinical potential in xerostomia. *Drugs* **49:** 143–155.