Efficacy of pilocarpine lozenge for post-radiation xerostomia in patients with head and neck cancer

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Abstract

Background: Patients with radiation-induced xerostomia produce little or no saliva. Several studies have demonstrated the efficacy of systemic administration of pilocarpine hydrochloride in individuals with post-radiation xerostomia. However, analysis of pilocarpine lozenges for treatment of post-radiation xerostomia in patients with head and neck cancer has not been reported.

Methods: The aim of this study was to quantify improvement in clinical symptoms and salivary function after treatment of post-radiation xerostomia with pilocarpine lozenges. In a double-blinded, placebo-controlled trial, 33 head and neck cancer patients were assigned randomly to receive Salagen® tablet, pilocarpine hydrochloride lozenge (3 or 5mg) or placebo lozenge every 10 days. At each visit, a subjective evaluation was undertaken through the use of visual analog scales before and at 180 minutes after treatment. Whole resting saliva was collected before and at 0, 30, 60, 90, 120, 150 and 180 minutes after treatment.

Results: The percentage of patients with decreased feeling of oral dryness, sore mouth or speaking difficulties after taking 5-mg pilocarpine lozenge was greater than Salagen® or placebo. There were statistically significant increases in salivary production in pilocarpine treatment groups vs. placebo (P<0.05).

Conclusion: The 5-mg pilocarpine lozenge produced the best clinical results, but further investigation with a larger group of patients is required.

Key words: Pilocarpine lozenge, post-radiation, xerostomia, head and neck cancer.

Abbreviation: VAS = visual analog scale.

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INTRODUCTION

Xerostomia may be defined as a subjective sensation of dryness of the oral mucous membranes.¹ It is a distressing condition which may result from a range of aetiologic factors. One of the aetiologic factors is iatrogenically induced following the administration of radiotherapy. Radiotherapy injures the parenchyma of the salivary glands, leading eventually to fibrosis and secretory hypofunction. The effects are dose-related and permanent, resulting in the condition known as post-radiation xerostomia.

Patients with radiation-induced xerostomia produce little or no saliva. As a result, they have oral discomfort and pain, greatly increased susceptibility to dental caries,²-⁴ frequent oral infections, and difficulty in speaking, chewing, and swallowing.⁵ These conditions can lead to severe oral disease and nutritional deficiencies. Although not life threatening in itself, xerostomia affects the quality of life of the sufferer and should not be considered a trivial complaint.

Several treatments for post-radiation xerostomia are ineffective. For example, nonpharmacologic approaches involve continual wetting with water or commercial solutions to lubricate the oral tissues. These methods, although successful in relieving the uncomfortable feeling associated with a dry mouth, are limited by the inconvenience of frequent administration, lack of continuity overnight, and inability to replicate the protective function present in endogenous saliva. Saliva substitutes are generally ineffective, and their degree of acceptance by patients in a long-term regimen is low.⁶

Pilocarpine hydrochloride is a direct acting cholinergic parasympathomimetic agent.⁷ It acts through direct stimulation of muscarinic receptors and can have broad, widely distributed effects on smooth muscle and exocrine tissues. Pilocarpine can stimulate salivary glands for an adequate length of time, can be administered by mouth, and has tolerable side effects.⁸ Several studies have demonstrated the efficacy of systemic administration of this drug in individuals with Sjögren's syndrome,¹¹,¹² and post-radiation xerostomia.¹³,¹⁴ Other studies, which also employed systemic administration of the drug, have shown pilocarpine to
be safe in dosages ranging from 2.5 to 10 mg.\textsuperscript{3,16} Although a low incidence of side effects, ranging from transient sweating, urinary frequency and headache, was reported in these trials, the effects were dose-dependent. Since an increased risk of side effects following systemic administration of pilocarpine may occur, topical pilocarpine may be an alternative. Local administration of pilocarpine offers several benefits: (1) it is easy to administer; (2) there is mechanical salivary stimulation; (3) it allows prolonged and increased topical contact; and (4) there is a potential decrease in systemic effects.\textsuperscript{17} However, the study of pilocarpine lozenges for treatment of post-radiation xerostomia in patients with head and neck cancer has not been reported. The aim of this study was, therefore, to evaluate the efficacy and safety of pilocarpine lozenge for the relief of xerostomia symptoms in individuals with salivary hypofunction due to radiotherapy for head and neck cancer. There were two sets of evaluations: (1) subjective self-rating visual analog scales (VAS) to quantify improvement in clinical symptoms and (2) salivometry to quantify salivary function.

**MATERIALS AND METHODS**

**Selection of study subjects**

Thirty-three head and neck cancer patients (22 males and 11 females) were recruited from a population of outpatients treated at the Division of Radiotherapy, Department of Radiology, Srinagarind Hospital, Faculty of Medicine, Khon Kaen University, Khon Kaen, Thailand. Inclusion criteria included: (1) patient aged between 20 to 60 years old; (2) completion of external radiation therapy, Cobalt-60 unit or 6MV Linear accelerator 6600 cGy/6.5 weeks, for more than six months before entry into the study; (3) patient experiencing clinically significant radiation-induced xerostomia for at least three months; (4) evidence of salivary flow upon stimulation with paraffin chew; and (5) signed informed consent. Exclusion criteria included: (1) a history of allergy to pilocarpine; (2) a history of xerostomia for less than three months; (3) patients who required or previously received tricyclic antidepressants or antihistamines with anticholinergic effects, beta blockers, or pilocarpine for ophthalmic indications; and (4) patients who had no evidence of salivary flow upon stimulation with paraffin chew. This project was approved by the Human Ethics Committee of Khon Kaen University (HE 44077). The procedures (possible discomforts or risks, as well as possible benefits), were fully explained to the patients and their informed consent was obtained prior to entry into the trial.

**Study design and treatment protocol**

A double-blinded, placebo-controlled, cross over design with repeated model measurement was used. After signing a consent form, all patients were assigned randomly to receive Salagen® tablet (MGI PHARMA, INC., Bloomington, U.S.A) which contains 5mg pilocarpine hydrochloride (positive control), pilocarpine hydrochloride lozenge (3 or 5mg) or placebo lozenge (negative control). Pilocarpine and placebo lozenges were of identical form, but the placebo contained no active drug. All lozenges were manufactured by the Department of Pharmaceutical Technology, Faculty of Pharmaceutical Sciences, Khon Kaen University. Each tablet of Salagen® or the lozenge was put in an envelope and coded. Each patient received four envelopes containing Salagen®, 3-mg or 5-mg pilocarpine or placebo lozenge and were asked to take part in a stimulation study every 10 days. Since the form of the Salagen® tablet is different from the lozenge, the examiner knew if the Salagen® tablet was selected. However, the remainder of the study was double-blinded. This compromise in blinding was used for proper drug administration.

All patients refrained from eating and drinking for one hour prior to the trial. On the first day of the experiment, the patients were interviewed about medication intake and general medical record. Oral complaints of the patients (dryness of the mouth, oral discomfort and the ability to speak) were assessed through the use of visual analog scales (VAS)\textsuperscript{14} before taking the medication. The pulse rate and blood pressure were recorded by a single person who used the same calibrated automated devices (Dinamap®, DPC 101x-EN Procare 100, Freiburg, Germany) and whole resting saliva was collected before drug administration (baseline). The patient then selected one drug from the four envelopes (containing Salagen®, 3-mg or 5-mg pilocarpine lozenge or placebo). If the Salagen® tablet was selected, the patients were instructed to take the tablet with a small glass of water. If the lozenge was selected, the patients were instructed to allow the lozenge to dissolve in the mouth without chewing. Subjective evaluation and salivary function analyses were carried out as described below. The remaining three envelopes were given to each patient on day 11, 21 and 31 after the first visit. Along with each stimulation, patients informed the examiner with regard to side effects (sweating, nausea, uropoiesis, flatulence and circulatory disorders) that were possible with the pilocarpine hydrochloride. The pulse rate and blood pressure were recorded again at 180 minutes after treatment.

**Subjective evaluation**

At each scheduled visit, subjective assessment of efficacy was undertaken before (baseline) and at 180 minutes after treatment using a 100mm VAS to record the response for each of three questions.\textsuperscript{18} Each of the questions evaluated a particular symptom, which was related to dryness (e.g., improvement in intra-oral dryness, oral comfort and ability to speak). The VAS was set up with negative responses “very dry”, “extremely uncomfortable”, or “very difficult” as the right anchor, and the positive responses, “not dry”, “comfortable”, or “easy” as the left anchor (Fig 1). The
patients marked on the scale their response relative to the two extremes. A patient with a decrease of at least 20 mm from baseline in the VAS score was classified as a “responder”.

Salivary function analyses

At each visit, whole resting saliva was collected eight times: pretreatment (baseline) and at 0, 30, 60, 90, 120, 150 and 180 minutes after treatment, by having patients expectorate saliva into a preweighed plastic cup for three minutes. The saliva-filled cups were weighed and the weight of the cups subtracted. All specimens were weighed to an accuracy of 0.0001 g.

Statistical methods

Descriptive statistics were calculated as follows: age of the patients was described in mean and standard deviation, and effect of the treatments on each symptom was in percent of response. Vital signs, blood pressure and pulse rate, as well as weight of saliva were analysed by using mean and 95 percent confidence intervals. Comparisons of the difference of mean weights of saliva and patients satisfaction in VAS among the four groups (pilocarpine lozenges, placebo and Salagen®) were analysed with a repeated measurement model for a continuous variable. The level required for statistical significance was P<0.05. Statistical analysis was performed using STATA version 7.0 BW.

RESULTS

Clinical outcomes

The 33 patients (mean age 51.9±11.4 years) satisfactorily completed the trial without any noted side effects. No statistically significant changes were found for blood pressure and pulse rate of all patients after treatment (Table 1). Oral dryness improved in 12.1, 63.6 and 69.7 percent of the patients receiving Salagen®, 3-mg and 5-mg pilocarpine lozenge, respectively, as compared with 42.4 percent of the patients receiving placebo (Table 2). Pairwise comparisons showed that the 5-mg lozenge group improved significantly more than the placebo group (P=0.03), whereas improvement in the 3-mg lozenge group was not significant (P=0.08). The Salagen® group had a lower proportion of improved responses than the placebo group (P=0.01) and both the 3-mg and 5-mg lozenge groups had higher proportions of improved responses than the Salagen® group (P=0.00 for both).

Among the patients who could be evaluated, improvement in oral comfort and speaking in the Salagen®, 3-mg and 5-mg lozenge groups was found, but not significantly different from the placebo group (Table 2).

Production of whole saliva

For the placebo, 3-mg and 5-mg lozenge groups, an increase in whole saliva production was observed after complete dissolution of the lozenge (at 0 minutes). Maximal weights of saliva after 3-mg and 5-mg lozenge administration were found at 60 to 90 minutes (Fig 2) and slowly declined thereafter. However, salivary output following placebo treatment (during 30–180 minutes) was slightly declined and stable. An increase in weight of saliva was seen within 30 minutes following Salagen® administration. This reached a maximum at 60 minutes and slowly declined thereafter. The Salagen®, 3-mg and 5-mg lozenge groups showed statistically significant increases in whole saliva production compared with placebo (Table 3). No significant difference was observed between the 3-mg and 5-mg lozenge groups and the Salagen® group.

DISCUSSION

The use of pilocarpine to treat salivary gland hypofunction is not a novel idea. Although several studies have demonstrated that oral administration of pilocarpine is effective in reducing the symptoms of radiation-induced xerostomia, no study has

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used the lozenge as a mechanism of delivery. The rationale for this manner of dispensing the drug is to obtain local stimulation of saliva production complementing systemic induced exocrine secretion. Data derived from this study have shown that pilocarpine lozenge more rapidly increased salivary production than Salagen®. Moreover, the percentage of the patients improved in the feeling of oral dryness, sore mouth and speaking after having taken 5-mg pilocarpine lozenge was greater than Salagen®. Subjective and objective improvements in the signs and symptoms of xerostomia in the patients may be due to the mechanical stimulation and local effects afforded by the lozenge because an increase in whole saliva production was observed after complete dissolution (at 0 minutes). Since Salagen® was orally administered, it acts predominantly directly on muscarinic receptors at end organ sites as a parasympathomimetic agent without local effects on minor salivary glands which have a wide distribution throughout the oral cavity. The time course of salivary response to Salagen® observed in this study is similar to that reported by Fox et al.10,11

The production of endogenous saliva, especially from the minor salivary glands, is of great benefit to the patients. Although minor salivary gland output is small (approximately 10 per cent of the total salivary output) compared with that of the major glands, they account for 70 per cent of the total mucin in saliva.20 Saliva mucins are reported to provide important protection of oral tissues from chemical and mechanical trauma and from infectious incursions and to provide lubrication via the rheologic properties of large mucin molecules in solution.21 Thus, minor salivary gland secretions play a major role in lubrication of the oral mucosa and are likely to contribute to the sensation of oral wetness and improvements in sore mouth and speaking.

CONCLUSION

Results from the present study are in agreement with previously published data that pilocarpine is effective in relieving symptoms of radiation-induced xerostomia and increasing whole salivary flow in many patients. Pilocarpine produces clinically significant benefits that clearly outweigh side effects and risks for symptomatic treatment of post-radiation xerostomia. In summary, patients taking 5-mg pilocarpine lozenge produced the best clinical responses when both safety and efficacy were considered, but further investigation with a larger group of patients would be required to provide more definitive information.

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REFERENCES


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