Use of Pilocarpine during Head and Neck Radiation Therapy to Reduce Xerostomia and Salivary Dysfunction

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Background. **Salivary gland hypofunction commonly develops during radiation therapy to the head and neck region. This study evaluated whether the sialogogue pilocarpine given during radiation therapy may reduce the severity of xerostomia and salivary dysfunction.**

Methods. **Nine patients requiring head, neck, or mantle radiation therapy participated in this double-blind, placebo-controlled trial. The patients took either 5 mg of pilocarpine or placebo four times daily for 3 months, beginning the day before radiation therapy. Subjective complaints and salivary functions were assessed.**

Results. **The pilocarpine-treated group had a lower frequency of oral symptoms during treatment than the placebo-treated group. Although salivary flow decreased in all patients, the pilocarpine-treated group had smaller reductions in flow. No drug effect was observed in glands that were irradiated completely. Thus, pilocarpine appeared to stimulate salivary tissues outside the radiation field.**

Conclusions. **These results suggest that stimulation with pilocarpine may reduce the severity of salivary dysfunction and associated oral symptoms during radiation therapy. *Cancer* 1993; 71:1848–51.**

Key words: xerostomia, radiation therapy, salivary gland, parotid gland, pilocarpine, sialogogue.

Normal salivary flow is essential to the health, function, and comfort of the upper alimentary tract. The major salivary glands often are included in head and neck fields of radiation therapy because of their anatomic position. Tumoricidal irradiation to the glands results in decreased salivary flow. This radiation-induced salivary dysfunction develops during radiation therapy, causing xerostomia and compromising oral intake.[1]

Stimulation of the glands during radiation therapy is recommended for preventing milder forms of radiation-induced salivary dysfunction, such as sialadenitis due to radioactive iodine therapy for thyroid tumors.[2] Chronic functional stimulation may ameliorate radiation-induced salivary gland damage because the toxic products accumulated in the glands may be cleared with saliva.[3]

This study evaluated whether the sialogogue pilocarpine, given throughout the course of radiation therapy, may reduce the severity of xerostomia and salivary dysfunction. Pilocarpine hydrochloride is a parasympathomimetic agonist that safely increases salivary flow for several hours[4] and has been shown to be effective in treatment of salivary hypofunction after radiation therapy.[5]

Materials and Methods

Ten patients were enrolled in this study, and 9 completed the protocol (Table 1). Patients scheduled to receive external-beam radiation therapy were considered if the major salivary glands would be completely (two patients) or partially included (eight patients) in the field. Before entry into the study, all patients had a complete medical evaluation and thorough assessment of salivary function. Patients with significant cardiovascular, pulmonary, hepatic, or pancreatic disorders or gastroduodenal ulcers were excluded for safety reasons. Women with childbearing potential were required to have a pregnancy test with negative results before entry and to use contraception during the study. All dentate patients had a rigorous preventive oral hygiene regimen including topical fluoride application. To ensure that all participants would respond to active drug, a 5-mg test

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Table 1. Patient Characteristics

Drug	Age (yr)	Sex	Tumor type (primary site)	Total tumor dose (Gy)
Pilocarpine	58	M	Squamous cell carcinoma* (base of tongue)	72
Pilocarpine	65	F	Mucoepidermoid carcinoma† (parotid gland)‡	59.4
Pilocarpine	44	M	Hodgkin disease† (cervical node)	45
Pilocarpine	22	F	Hodgkin disease† (cervical node)	40
Pilocarpine	24	M	Hodgkin disease† (cervical node)	39.6
Placebo	53	F	Squamous cell carcinoma* (nasopharynx)	70
Placebo	29	F	Hodgkin disease† (cervical node)	45
Placebo	21	M	Hodgkin disease† (supraclavicular node)	41
Placebo	42	M	Malignant lymphoma† (cervical node)	30.6
Placebo	56	M	Malignant lymphoma† (inguinal node)§	22.9

* Salivary glands were entirely within the field of radiation.

† Salivary glands were partially irradiated.

‡ The affected parotid gland was resected. Opposed lateral ports were irradiated. Contralateral parotid was used for flow rates.

§ Patient received tumoricidal radiation to abdominal and pelvic ports. After 22.9 Gy to mantle field, radiation was suspended because of thrombocytopenia. Patient was removed from study and the data were not used.

dose of pilocarpine was given and salivary output was monitored.

Patients were randomized in a double-blind manner to receive either 5 mg of pilocarpine hydrochloride or placebo. Capsules were prepared by the National Institutes of Health Pharmaceutical Development Service and dispensed in coded bottles. Drug treatment began the day before radiation therapy and continued for 3 months. Patients were instructed to take one capsule four times daily. The time of drug intake was adjusted so that the stimulatory effect of pilocarpine would occur during the radiation therapy session, with the assumption that peak salivary flow occurred at 1 hour after dose.[6] This protocol was in accordance with the ethical standards of the Institutional Review Board of the National Institute of Dental Research.

Patients returned weekly during radiation therapy, which continued from 4 to 8 weeks. Examination was repeated at 3 months (end of drug treatment) and 4, 5, 6, and 12 months. Each visit included subjective and objective assessments of salivary function. A standardized questionnaire was administered by the clinician, and major salivary gland flow rates were determined as previously described.[7] A Carlson-Crittenden cup was used to obtain parotid saliva. Submandibular/sublingual saliva was collected with a standardized suction device. Saliva was collected during a resting state (unstimulated function) and after a 2% citric acid stimulus (stimulated function). If a given flow measure was not observed within 5 minutes, it was assumed to be zero.

Frequency data of subjective responses were compared by the Fisher exact test. To correct for the wide variation in normal salivary function, the *change* in salivary flow rate was calculated for each patient by subtraction of baseline values before radiation therapy from flow rates during and after radiation therapy. The Student t or Mann-Whitney U test was used to assess differences between the pilocarpine-treated and placebo-treated groups. An alpha level of 0.05 was accepted as statistically significant.

Results

Subjective Findings

None of the participants had subjective complaints of oral dryness (xerostomia) before radiation therapy. All reported that the mouth felt drier after radiation therapy was started. The pilocarpine-treated group reported significantly fewer oral symptoms than the placebo-treated group during drug treatment. For example, when asked "Does your mouth feel dry when you are eating?" 27% of responses were "yes" among the pilocarpine-treated patients during drug treatment (14 responses of yes for the 52 times the question was asked). The frequency of this symptom was 84% for the placebo-treated group (31 responses of yes for the 37 times the question was asked; $P < 0.0001$). Similarly, when asked "Do you sip liquids with meals to aid in your swallowing?" 37% of responses (19 of 52) were positive in the pilocarpine-treated group, whereas 78% (29 of 37) answered "yes" in the placebo-treated group ($P < 0.0001$). After drug treatment, the frequency of oral complaints generally decreased, and by 1 year their combined frequency was approximately 25% in both groups.

Pilocarpine was well tolerated at this dose and schedule. The use of pilocarpine did not alter cancer therapy in any patient. All tumors responded favorably to radiation therapy and were in complete remission for the remainder of the study.

Objective Findings

Salivary flow decreased in all patients within the first week of radiation therapy. Decreases in function persisted throughout the year of study. However, the group taking pilocarpine had smaller losses in stimulated function than the placebo-treated group (Fig. 1). The difference in stimulated parotid function between groups was statistically significant at the 3-month examination. Unstimulated flows showed a similar pattern of immediate, sustained decrease, but there was little difference between the pilocarpine-treated and placebo-treated groups (data not shown). It should be mentioned that salivary function declined to nil during radiation therapy in the two patients whose glands were irradiated completely with a high dosage (denoted by an asterisk in Table 1). Thereafter, neither patient responded to citric acid or pilocarpine.

Discussion

Although the small number of patients limits interpretation of our results, this study merits attention because both the subjective and objective assessments suggest that pilocarpine given during radiation therapy has clinical benefit. First, the frequency of subjective complaints during drug treatment was significantly lower in the pilocarpine-treated group than the placebo-treated group. Specifically, the pilocarpine-treated group perceived an enhanced ability to comfortably manipulate a food bolus and swallow solids without additional liquids. A lower frequency of xerostomia and dysphagia during radiation therapy would be clinically advantageous in improving oral intake. Other subjective parameters such as food enjoyment and quality of life also could be enhanced.

Second, the group taking pilocarpine exhibited smaller decreases in stimulated salivary function than the placebo-treated group during drug treatment. Stimulated salivary flow is clinically important for lubricating oropharyngeal structures during mastication and deglutition and for physical cleansing and chemical buffering in the upper gastrointestinal tract.[8] Significantly less compromise in parotid function was observed in the pilocarpine-treated group (Fig. 1). Some parotid tissue was shielded in three of the five patients receiving pilocarpine. Pilocarpine had no apparent effect on glands that were irradiated completely with a high dose (see Results). Given that all salivary tissue directly within the field is affected by radiation[9] and that the degree of salivary dysfunction is directly dependent on the volume of salivary tissue exposed,[10-12] these results suggested that pilocarpine was stimulating the salivary tissue outside the field. If the portal arrangement or patient positioning will allow some gland tissue to be spared, the use of pilocarpine during radiation therapy may reduce the resultant salivary dysfunction. The sequelae of severe salivary dysfunction, such as candidiasis, esophagitis, and high dental caries risk,[13-15] may be ameliorated by maintaining better salivary function. We believe additional study of pilocarpine administration during radiation therapy is warranted.

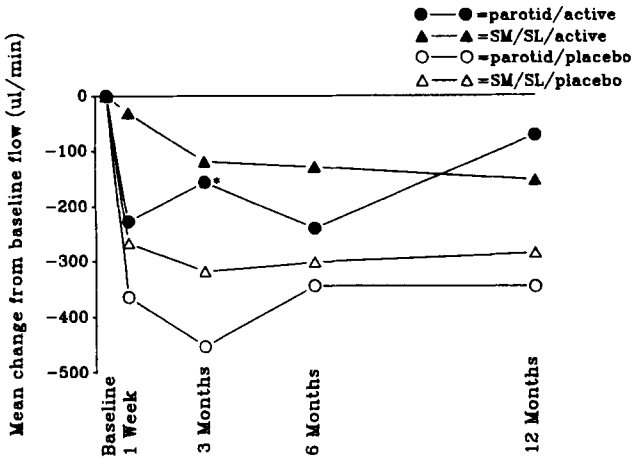

Figure 1. Changes in stimulated salivary flow rates during study. The group mean corrected for baseline flow is illustrated for patients taking pilocarpine (n = 5) and placebo (n = 4). Drug treatment was initiated the day before radiation therapy began and continued daily for 3 months. The difference in stimulated parotid function between groups was statistically significant at the 3-month examination (*P = 0.025). SM/SL: submandibular/sublingual.

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