Effectiveness of Pilocarpine in Postradiation Xerostomia

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Pilocarpine and placebo tablets were administered for 90 day periods in a double-blind, sequential crossover trial to 12 patients with postradiation xerostomia. Salivary flow was measured by two techniques, symptomatic change and adverse side effects were also recorded. Nine of the 12 patients showed marked improvement by two or more criteria while taking pilocarpine. None of the 12 patients showed meaningful improvement while on placebo. Side effects were minimal and easily controlled. These results show that pilocarpine is effective in relieving the signs and symptoms of postradiation xerostomia.

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APPROXIMATELY 27,500 NEW CASES of primary malignant neoplasms of the oral cavity and pharynx are diagnosed each year in the United States.[1] Most patients undergo radiation therapy, either as the sole means of treatment, or in combination with preradiation or postradiation surgery or chemotherapy. Chronic xerostomia is a complication met by almost all patients who have radiation therapy in the region of the head and neck. Its severity is approximately proportional to the amount of salivary gland tissue in the primary beam and the amount of radiation administered.[2–4] It is generally severe and essentially permanent; although some salivary gland function returns in time, it never approaches its former level. Chronic xerostomia creates many clinical problems for affected patients. They find it very difficult to chew, swallow, or enjoy food, to talk for any length of time without needing water, or to wear removable dentures with comfort. In addition, they become susceptible to chronic oral overgrowth by *Candida* species and to a severe and rapidly progressive form of dental caries.

Current therapy for postradiation xerostomia includes topical fluorides to retard caries, and saliva substitutes (water, artificial saliva) and sialogogues to improve oral function and comfort.[5] Taking frequent small sips of water relieves the symptoms for some patients, but imposes upon them the inconvenient, and possibly embarrassing, necessity of carrying around a small bottle of water. It may also lead to urinary frequency and nocturia. Artificial saliva has been of some help, mostly to patients wearing removable dentures.[6] Occasionally some people will experience symptomatic relief from sucking on sugarless sour hard candies or from chewing sugarless gum.

Pilocarpine is a potent cholinergic drug.[7,8] It appears to act by direct cell stimulation rather than by disturbing the cholinesterase-acetylcholine relationship. Currently the drug is used topically in the eyes as a miotic. Since pilocarpine works by neural stimulation, its side effects are those of an exaggerated response by some systems. Common dose-related side effects of systemic administration include increased sweating and gastric motility. The fatal dose of pilocarpine is unknown, but 100 mg may be viewed as a dangerous amount. Toxic reactions are characterized by exaggerated parasympathomimetic effects.

Although the effectiveness of pilocarpine in stimulating saliva in people with essentially normal salivary glands is well established, it was not known how well the drug would work in patients whose glands had been damaged by radiation. In this article we report the results of a double-blind study comparing the effects of pilocarpine tablets and placebo on salivary flow rate in patients who had received therapeutic radiation for head and neck cancer.

Materials and Methods

The 12 subjects in this study were drawn from patients seen in the Oral Medicine Clinic at the University of California, San Francisco (UCSF), during and after radiation treatment. Four patients had been treated for carcinoma of the anterior tonsillar pillar; three for carcinoma of the nasopharynx; two for carcinoma of the tongue; two for carcinoma of the floor of the mouth; and one for carcinoma of the maxillary antrum. All had received between 5500 and 8000 rad of external radiation at the rate of 180 rad per day, 5 days per week; and in each case the parotid glands were completely within the primary beam. All were experiencing severe xerostomia 6 months after radiation therapy had been completed. The patients ranged in age

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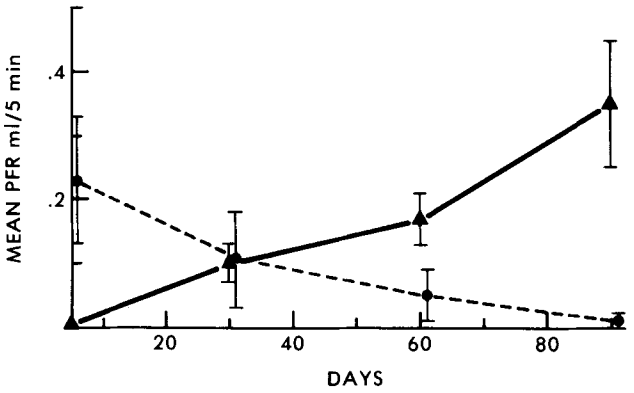

FIG. 1. Stimulated parotid flow rate (PFR) after crossover. Solid line represents patients receiving pilocarpine and broken line represents patients receiving placebo. Bars show standard deviation.

from 16 to 79 years. Their informed consent was obtained after the nature of the procedures and possible discomforts and risks had been fully explained.

Subjects received either 2.5 mg tablets of pilocarpine HCl, or a placebo of identical appearance, manufactured and randomized by the UCSF Pharmaceutical Technology Laboratory. By double-blind random assignment, six patients initially received pilocarpine and the others received placebo. Each preparation was used for 90 days, and then each patient was crossed over to the other preparation for another 90 day period. Patients received a supply of tablets and took from 2 to 3 tablets, three to four times each day. Dosage was based on the patient's weight and extrasalivary side effects, and was reduced in those patients who experienced excessive sweating or abdominal cramping.

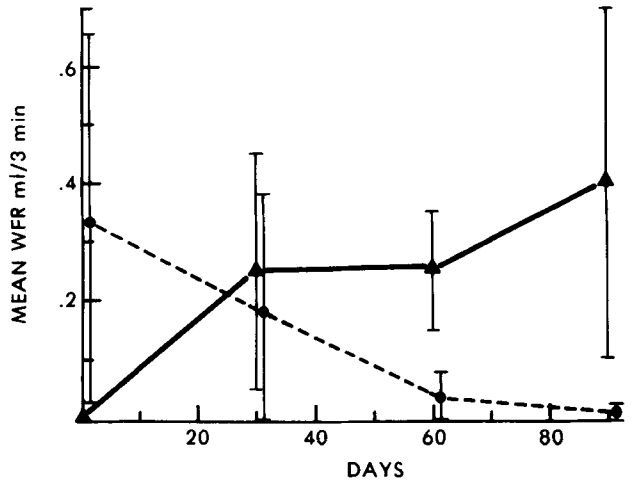

FIG. 2. Whole salivary flow rate (WFR) after crossover. Solid line represents patients receiving pilocarpine and broken line represents patients receiving placebo. Bars show standard deviation.

We evaluated each patient quantitatively by salivary flow rate measurements and qualitatively by the appearance of the oral mucosa and saliva, as well as by the patient's symptoms at the beginning, at 30 day intervals, and at the end of the study. To avoid measuring direct drug effects, we discontinued the test drug 24 h before each assessment. Salivary function was assessed by: (1) standardized 5 minute stimulated parotid flow rate; (2) stimulated whole salivary flow rate; and (3) subjective evaluation by patients.

To measure parotid flow rate, we placed Carlson-Crittenden cups bilaterally over the opening of Stenson's ducts, then stimulated secretion by applying a 1:1 dilution of commercial lemon concentrate (Borden, Columbus, Ohio) with a cotton-tipped applicator to the posterior sides of the tongue. Stimulation was applied for 5 seconds, at 30 second intervals during the 5 minute collection period. The saliva passed through polyethylene tubes into graduated centrifuge tubes, and the saliva remaining in the polyethylene tube at the end of the collection period was forced into the centrifuge tube with compressed air.[9] To determine stimulated whole salivary flow rate, we had the subjects chew paraffin wax for 3 minutes and expectorate at will into a measuring cylinder. All collections were made in the morning by the same operator. The subjects had not been fasting. In addition, at each visit we asked the subject to comment on the severity of his or her dryness of mouth, and to assess subjectively the effectiveness of each preparation.

Results

During their period on pilocarpine, the subjects as a group showed a measurable increase in parotid flow rate. Conversely, when they received placebo, parotid flow rate was low (Fig. 1); the difference was not significant at 30 and 60 days but was significant at 90 days ($P < 0.005$, Mann-Whitney U test).

With whole flow rate the results were similar but less striking. Whole flow rate was minimal during placebo administration and showed a small but sustained increase during administration of pilocarpine (Fig. 2). Again the difference was not significant at 30 or 60 days, but was significant at 90 days ($P < 0.05$, Mann-Whitney U test).

When the effectiveness of pilocarpine at 90 days was compared with that of placebo in individual patients, we found that five of the 12 subjects showed improvement by all three criteria; four showed improvement by two criteria; two showed improvement by one criterion; and only one patient showed no improvement at all. Nine of the twelve subjects showed symptomatic improvement while on pilocarpine, but while taking placebo, only two subjects showed improvement by a single criterion, and none by two or more criteria. Ten of 12 subjects failed to

show any improvement at all while on placebo. Chi-square analysis showed that the probability of this happening by chance was very low ($P < 0.001$).

One subject complained of sweating and abdominal cramps, and five others complained of mild sweating. None of the complaints was serious enough to warrant discontinuing the study. When the code was broken, it was revealed that all complaints occurred while the patients were on the active drug. Two subjects needed to have the dose reduced to 2.5 mg per dose.

Discussion

Recently Fox *et al.*[10] described a double-blind placebo-controlled study of the efficacy of oral pilocarpine for dry mouth in six patients, of whom two had primary Sjogren's syndrome and four had objectively confirmed xerostomia but nonspecific abnormalities in labial salivary gland biopsies. They showed that a daily dose of 5 mg pilocarpine for 2 days was useful and relieved the sensation of oral dryness.

Our small scale, 6 month study using a double-blind sequential crossover design has shown that nine of 12 patients with postradiation xerostomia experienced significant improvement in salivary flow while receiving pilocarpine, whereas ten of the 12 showed no such improvement while receiving placebo. Side effects were minimal and easily controlled. We do not, however, use this drug in patients who have a current or recent past history of gastrointestinal ulcer, labile hypertension, or severe cardiovascular problems.

As Figures 1 and 2 show, some subjects taking placebo started their period on that preparation with a higher flow rate. This was because they had been taking pilocarpine for the previous 90 days.

The slightly less remarkable results found with whole salivary flow (Fig. 2) are not surprising, and are probably due to the technical difficulties encountered with this method, such as the high viscosity of whole saliva in these patients, foaming, and the small quantities collected.

We believe that these results justify the use of pilocarpine, under careful supervision, for patients with postradiation xerostomia. For our study, we administered the pilocarpine in tablet form for purposes of convenience and accuracy, and in order to present patients with an active preparation that was indistinguishable from placebo. For continued use we now prescribe a 1 mg/ml solution of pilocarpine hydrochloride in water, without flavoring syrup, because it is widely available and easy to administer; the adult dosage range is from 2.5 to 7.5 mg two to four times a day. We have treated over 200 patients in a noncontrolled clinical setting with pilocarpine HCl solution, and continue to find the drug useful in decreasing symptoms.

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