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# Reducing the Incidence of $^{131}\text{I}$ -Induced Sialadenitis: The Role of Pilocarpine

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The goal of this study was to reduce the salivary symptoms of pain and xerostomia caused by  $^{131}\text{I}$  therapy for papillary and follicular thyroid carcinoma. **Methods:** In a single-blind controlled prospective study of 60 patients, we investigated whether pilocarpine, 5 mg orally every 8 h for 1 wk after  $^{131}\text{I}$  therapy, would reduce salivary symptoms. All patients received 8 mg of dexamethasone and 100 mg of dolasetron mesylate orally 2 h before therapy and every 12 h for another 5 doses after  $^{131}\text{I}$  ingestion. In addition, for a week after therapy all drank 2,400 mL of nondairy liquid per day and had sugar-free gum or candy in their mouths at all times when awake for a week and, for the first 3 nights, every 3 h after retiring. All brushed their mouths out every 3 h while awake and also for the first 3 nights after  $^{131}\text{I}$  therapy. Symptoms and signs were followed by frequent telephone calls over the first week and every 8–12 wk thereafter, a physical examination within the first 10 d after therapy, and a clinic visit 6–8 mo after therapy. Statistical comparisons were by  $\chi^2$  analysis. **Results:** The 2 patient groups were not statistically different in age, sex, type of thyroid cancer, or  $^{131}\text{I}$  activity administered ( $P > 0.05$ ). There were no statistical differences between the groups in the prevalence of sialadenitis, stomatitis, xerostomia, or dysgeusia over the next 6 mo ( $P > 0.05$ ). **Conclusion:** Under the conditions of the study, pilocarpine did not reduce the occurrence of radiation sialadenitis or stomatitis. The occurrence, however, was lower than had previously been reported in the literature, possibly because of the concurrent stringent application of physiologic sialogogues (candy, gum, fluids), dexamethasone, and dolasetron mesylate, a serotonin receptor antagonist.

**Key Words:**  $^{131}\text{I}$ ; radiation sialadenitis; pilocarpine; serotonin receptor antagonist

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**O**ral high-dosage  $^{131}\text{I}$  for the ablation of postthyroidectomy remnants and the treatment of functioning papillary and follicular thyroid carcinoma carries the risk of several adverse reactions, some of which—such as significant myelosuppression—are fully preventable. Other adverse deterministic reactions include nausea and vomiting, painful

neck swelling, laryngeal nerve damage, oligospermia or aspermia, radiation pneumonitis, xerophthalmia, epiphora, glossitis, and stomatitis. Sialadenitis may also occur, with painful, swollen salivary glands, not infrequently leading to some degree of xerostomia (1). The first case report of “radiation sialitis” from  $^{131}\text{I}$  appeared in 1955 (2). Recent reviews of salivary effects after  $^{131}\text{I}$  therapy have noted an incidence of acute sialadenitis ranging from 24% to 67%, with chronic sialadenitis in 11%–43% of those treated (1,3–7).

This study sought to determine whether the occurrence of painful acute sialadenitis and, hopefully, the chronic salivary pain syndrome could be reduced in patients receiving the sialogogue pilocarpine, compared with a control population.

## MATERIALS AND METHODS

This study, following the guidelines of the University of Cincinnati Institutional Review Board, examined the response of 60 consecutive patients referred to the Eugene L. Saenger Radioisotope Laboratory, Department of Radiology, of the University of Cincinnati Medical Center for ablation of thyroid remnants after thyroidectomy or for the treatment of recurrent or metastatic papillary or follicular carcinoma of the thyroid. None of the patients had a preexisting salivary condition, including rheumatoid arthritis, Sjogren’s syndrome, lymphoma, or AIDS, and none was taking an anticholinergic drug.

Patients were randomly assigned to receive sialorrheic therapy with or without pilocarpine, 5 mg every 8 h orally for 1 wk. All patients were asked to keep a log of any new symptoms after  $^{131}\text{I}$  therapy. All received a consent form for treatment with  $^{131}\text{I}$  for ablation of thyroid remnants or metastatic disease. This consent form listed all adverse reactions to radioiodine therapy, indicated that some medications the patient was to receive might reduce the occurrence of some of the symptoms, but did not indicate which medication would be a sialogogue.

All patients received 8 mg of dexamethasone and 100 mg of the serotonin subtype 3 receptor antagonist dolasetron mesylate (Anzemet; Aventis Pharmaceuticals, Inc.) 2 h before their  $^{131}\text{I}$  therapy and every 12 h for another 5 doses after  $^{131}\text{I}$  ingestion. The patients fasted for 3 h after therapy, both to ensure complete absorption and to reduce any risk of nausea and vomiting. All were then instructed to have sugar-free hard candy or gum in their mouths at all times when awake for 1 wk. In addition, all patients were awakened every 3 h for the first 3 nights, first to urinate, then to chew a piece of gum or suck candy, and finally to gently brush the oral mucosal surfaces with a soft toothbrush and water for 1 min and then expectorate.

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A family member was always involved in the discussion of therapy to be sure it was carried through, and the investigator called each patient at least once during the week after therapy for the same purpose. Each patient also ingested at least 2,400 mL (ten 8-oz glasses) of nondairy liquid daily during the week after therapy. Each patient received frequent phone calls over the first week and every 8–12 wk thereafter for the next 6–8 mo and was examined by the investigator 4–10 d after therapy when the patient returned for the posttherapy whole-body scan using the therapy dose of  $^{131}\text{I}$ . Each was asked directly about the presence of xerostomia at this time and at the 6- to 8-mo follow-up scan. Specifically, each was asked if there had been an increase in dryness of the mouth, if there was an increase in production of thicker mucus or morning expectoration, and if the patient could chew and swallow without drinking. Salivary scintigraphy and other quantitative measures of saliva output were not used.

Patients were also quizzed about the presence of cholinergic side effects and other adverse events that have been attributable to pilocarpine, including excessive perspiration, flushing, or chills; anorexia, diarrhea, nausea, or vomiting; rhinitis; urinary frequency; dizziness; headache; and psychologic effects such as anxiety, confusion, and abnormal dreams. All comparisons were performed with  $\chi^2$  analysis.

## RESULTS

Twenty-eight patients received pilocarpine and 32 did not. There was no significant difference between these 2 randomly assigned groups in age, sex, type of functioning thyroid cancer (papillary or follicular), or mean dosage of  $^{131}\text{I}$  administered (Table 1).

Table 2 summarizes the results of the study. Acute sialadenitis (swollen, painful salivary glands) within a few days after therapy never occurred in either group, although 1 patient in the pilocarpine group and 2 who did not receive pilocarpine had mild salivary tenderness on palpation in the first 4–10 d after therapy. This difference was not significant ( $P > 0.05$ ). One patient in the pilocarpine group, but none in the control group, had an onset of recurrent discomfort at 4 mo after  $^{131}\text{I}$  therapy. Swelling and discomfort of the right

**TABLE 1**  
Patient Demographics

Parameter	Pilocarpine	No pilocarpine
Number of patients		
Women	25	23
Men	7	5
Age (y)		
Mean	47.3	46.6
SD	17.0	16.5
Cases of thyroid carcinoma		
Papillary	28	25
Follicular	4	3
$^{131}\text{I}$ activity (GBq)		
Mean	4.40	4.92
SD	1.42	1.92

For all comparisons,  $P > 0.05$ .

**TABLE 2**  
Symptoms After  $^{131}\text{I}$  Therapy

Symptom	Pilocarpine (n = 32)	No pilocarpine (n = 28)
Sialadenitis		
Acute	1 (3%)	2 (7%)
Chronic	1 (3%)	0
Stomatitis or glossitis	5 (16%)	6 (21%)
Subjective xerostomia	0	0
Dysgeusia	2 (6%)	1 (4%)

For all comparisons,  $P > 0.05$ .

parotid gland occurred just before or during meals, and manual massage was required to relieve the symptoms. We interpret this symptom complex as chronic sialadenitis.

Despite the mechanical removal of  $^{131}\text{I}$  by a soft toothbrush and expectoration every 3 h for the first week (and for the first 3 nights as well), both sets of patients experienced a low incidence of mild glossitis or stomatitis (16% and 21%, respectively,  $P > 0.05$ ), with fewer than 10 small oral ulcers per patient identified on physical examination. Both groups also had a small, statistically insignificant, onset of dysgeusia, which resolved by 6 mo in all patients.

The pilocarpine group did experience a few side effects not noted in the control group. Three patients believed they were perspiring more than normally. One had a psychologic reaction that he described as an out-of-body experience, which resolved within 12 h of his discontinuing pilocarpine. No patients in either group had new gastrointestinal or urinary symptoms.

## DISCUSSION

We report here the efficacy of our approach to oral stimulation of the salivary glands. These data are consistent with the findings of our earlier unpublished retrospective study on salivary toxicity using the same prophylactic regimen, which we applied to 109 patients after  $^{131}\text{I}$  therapy. None of these patients complained of salivary gland pain, and 11 experienced glossitis or stomatitis.

Adding pilocarpine to the physiologic sialogogues used in our therapeutic regimen for thyroid cancer did not alter the low rate of occurrence of radiation sialadenitis in the 2 groups. However, both groups experienced less sialadenitis than the previously reported range—24%–67%—for prospective studies (1,3–7). Alexander et al. have noted, as we have with these current data, that patients using pilocarpine medication had no fewer symptoms than did those not using the drug, but these authors provided no data on the dose of pilocarpine, the randomness of assigning this secretagogue, or how long it was taken (5).

Our regimen included allowing nothing by mouth for 3 h after  $^{131}\text{I}$  therapy, both to ensure complete absorption and to avoid having the patient ingest anything that might cause

nausea or vomiting. We insisted, always with family collaboration, that the patient suck candy (any type not containing FD&C red dyes 3 or 28, which are heavily iodinated) or chew gum at all times when awake for 7 d. We also had the patient awakened at home every 3 h for the first 3 nights, overseen by a family member, to suck or chew a single piece of candy or gum, respectively, presumably providing significant sialorrhea that the cholinergic agonistic pilocarpine apparently could not increase further, at least for the clinical effects we observed. Hydration is, of course, important for salivary secretion, and we demanded that patients ingest at least 2,400 mL (ten 8-oz glasses) of nondairy liquid per day for a week.

Although dexamethasone was given at high doses for its antiemetic effect, the antiinflammatory effects of such doses are well known and could potentially reduce sialadenitis. We also used dolasetron mesylate, a selective serotonin subtype 3 receptor antagonist, for its antiemetic properties. No vomiting occurred in any patient. In addition, because serotonin has been shown to decrease salivary flow in a mammalian model (8), this serotonin antagonist, administered both before and every 12 h with dexamethasone for 3 d after  $^{131}\text{I}$  therapy, may well have been another sialogogue in these patients in addition to hydration and candy or gum.

When acute salivary gland inflammation occurred, it was mild, and tenderness was evoked only on direct palpation in just 3 patients, none of whom was experiencing spontaneous salivary gland pain. With such a low rate of occurrence in the control group, it is not surprising that pilocarpine was not found to improve on this effect at the statistical power of this study.

No patient in the current prospective study noted xerostomia up to at least 8 mo after therapy, with follow-up on 30% of these patients for 5 y. In other studies not using our prophylactic regimen, subjective xerostomia after  $^{131}\text{I}$  therapy for thyroid cancer has been noted in 22%–54% of patients (5,9–12), with painful sialadenitis in 24%–67% (1,3–7). One study reported a lower occurrence—only 12% of patients with  $^{131}\text{I}$ -induced radiation sialadenitis—probably because the diagnosis was made only if the patients reported it retrospectively; they were not prospectively questioned by the authors (13).

The symptoms of radiation-induced xerostomia show little correlation with measured salivary flow rates (14,15). Of patients with subjective xerostomia, 14%–31% have actually had normal salivary function when dynamic salivary scintigraphy was used (16,17). Bohuslavizki et al. saw abnormal scintigraphic findings in all their patients receiving high doses of  $^{131}\text{I}$ , noting that these objective findings were therefore not predictive of clinically relevant xerostomia (16). Similarly, Nakada et al. found patients showing disagreement between subjective symptoms and salivary gland scintigraphy (17). Hence, we did not measure salivary function with objective techniques such as saliva collection or scintigraphy.

All authors agree that the rate of signs and symptoms increases with the cumulative activity of  $^{131}\text{I}$ , but the available literature does not allow a metaanalysis with reliable

plotting of a dosage–response curve for this deterministic effect, because of the different ways the clinical and physiologic observations were made in different centers.

The drug amifostine, whose active thiol metabolite scavenges reactive radiation-induced oxygen species, can reduce the incidence of xerostomia (16,18). However, amifostine is expensive and must be infused intravenously over 15 min. In addition, its list of side effects at a dose of 910 mg/m<sup>2</sup> includes nausea and vomiting in up to 88% (grade 3 or 4 in 9%) and hypotension in 27%. Hence, we dismissed the use of amifostine for this study.

The timing of the use of candy as a sialogogue became controversial recently when Nakada et al. found less sialadenitis and xerostomia if lemon candy was begun at 24 h instead of 1 h after radioiodine therapy (17). However, 81% of the group waiting 24 h for candy received steroids or ibuprofen for radiation sialadenitis, versus 52% in the group who began sucking lemon candy 1 h after therapy (19), yet, paradoxically, the reported incidence of sialadenitis in the paper of Nakada et al. was higher in the early–candy-sucking group (64%) than in the late-sucking group (37%). The sialorrhic prescription of Nakada et al. was less stringent than ours. We required 7 d of constant sucking or chewing, as well as sucking or chewing every 3 h for the first 3 nights, whereas Nakada et al. asked that the patient suck lemon candy only every 2–3 h over 5 d, without nocturnal salivary stimulation.

Our study had several limitations. Salivary function was not studied objectively, but because there was a disconnect between the physiologic findings reported after  $^{131}\text{I}$  and related symptoms, this limitation does not seem to detract from our findings. Each patient was asked about the presence of a dry mouth in a binary, “present or absent” mode, whereas a more sophisticated analysis might have used a visual analog scale and noted more subtle changes in the patient’s perception of a dry mouth. Also, our report describes the results of all patients followed only to 6–8 mo, although some have been followed for 5 y. A study with a longer follow-up is in process but is not yet completed. We did not include a control group without any of the drugs or physiologic sialogogues we used, because of the expected unacceptably high incidence of acute sialadenitis in patients with no prophylaxis (24%–67% (1,3–7)). Finally, if the reduction in radiation sialadenitis had been less dramatic, this study would have been insufficiently powered to detect the effect of our prophylactic regimen.

## CONCLUSION

Our attempt to reduce the occurrence rate of  $^{131}\text{I}$ -induced radiation sialadenitis using the cholinergic drug pilocarpine to stimulate salivary flow was unsuccessful, probably because of the strong sialorrhic effect of the other measures used: oral sialogogues (candy and gum used constantly over a week and every 3 h for the first 3 nights), oral hydration to at least 2.4 L/d, a serotonin receptor blocker (as an antiemetic but also as a secretagogue), and the antiinflammatory and

antiemetic dexamethasone. The occurrence rate and severity of radiation sialadenitis when using this “Cincinnati” regimen were less than has been found by any prospective study reported in the medical literature.

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