Lemon juice stimulation of salivary-gland flow increases the absorbed doses of ^{131}I to the salivary glands after the administration of ^{131}I

Jentzen W, Balschuweit D, Schmitz J, Freudenberg L, Eising E, Hilbel T, Bockisch A, Stahl A. The influence of saliva flow stimulation on the absorbed radiation dose to the salivary glands during radioiodine therapy of thyroid cancer using (124)I PET(/CT) imaging. Eur J Nucl Med Mol Imaging 2010. July 13 [Epub ahead of print.] 10.1007/s00259-010-1532-z [doi]

SUMMARY

BACKGROUND

Radioiodine therapy with ^{131}I is taken up by target tissues, including tumors and thyroid remnants, but is also taken up by the submandibular and parotid salivary glands. As a result, high levels of ^{131}I therapy may be associated with salivary-gland damage, leading to long-term side effects, including sialadenitis, which occurs in about 30% of patients, and xerostomia, which has an incidence of about 10 to 20%. Several radioprotective procedures have been proposed for this problem, but perhaps the most common approach for this problem is the use of sialogogic agents such as lemon juice to increase saliva flow by stimulating salivary glands. Although several studies suggest that sucking or chewing on lemon slices during ^{131}I therapy decreases the effect of radiation on the salivary glands, a recent prospective study sparked controversy about this practice by finding that sucking lemon candies induced a significant increase in the frequency of sialadenitis and xerostomia, as compared with a 24-hour delayed stimulation. Moreover, the current ATA guidelines recommend that there is no objective proof that stimulation with lemon juice prevents radiation damage to the salivary glands, whereas the European Association of Nuclear Medicine recommended this practice in their recent guidelines. The aim of the present study was to assess the effect of chewing lemon slices on the absorbed radiation doses to the salivary glands.

METHODS AND STUDY SUBJECTS

Study Subjects

The study subjects were 10 patients referred to the author's clinic to receive an ^{124}I positron-emission tomographic/computed tomographic (PET/CT) scan after having been treated with thyroidectomy for differentiated thyroid cancer. Excluded from the study were patients with a history of salivary gland disease or treatment with external-beam radiotherapy to the neck or head or who were taking medication that would affect salivary flow such as anticholinergic, beta-blockers, or antidepressants. Prior to their first ^{131}I treatment, the serum thyrotropin (TSH) levels were stimulated by thyroid hormone withdrawal or by recombinant human TSH (rhTSH) injections. Before imaging, TSH levels were ≥25 μl/ml and the mean (±SD) ^{124}I activity was 26.5±3.3 MBq (range, 22.6 to 30.5).

Patient Study Protocols

The study comprised a stimulation and a nonstimulation protocol. Ten patients in the stimulation group chewed lemon slices for approximately 20 minutes after ingesting a capsule containing ^{124}I. This group continued chewing lemon slices over the first day. Approximately 10 minutes elapsed between stimulation and emission scans. The patients ate lunch after 2 to 4 hours, a snack after 6 to 7 hours, and dinner 9 to 10 hours after ^{124}I administration. The patients in the nonstimulation group did not chew lemon slices during the ^{124}I pretherapy procedure and were not permitted to have food or drink until after completion of the last PET scan on the first day, approximately 4 hours after ^{124}I administration. Thereafter, the patients ate a snack and had dinner at about the same time as the stimulation group, and the food composition was almost identical in the two study groups.

Salivary-Gland Dosimetry Protocol

Patients had a series of six stand-alone scans (Exact HR+ PET) and one PET/CT scan. Stand-alone PET imaging was performed at approximately 0.5, 1, 2, 4, 48, and ≥96 hours after oral intake of a capsule containing $^{124}INaI$. Imaging at approximately 24 hours was performed using the PET/CT system. On the stand-alone PET system, emission and transmission times per bed position were 300 seconds and 120 seconds, respectively. The PET/CT scans also lasted 300 seconds, and the CT acquisitions were as follows: 130 m as effective tube current, 130 kVp tube voltage, 5 mm slice width, 0.08 second rotation time, and a prerotation table speed of 8 mm.

Blood-Count Protocol

The radioiodine kinetics in blood were determined by measuring the activity concentration for each patient's blood samples taken at different time points following ^{124}I administration. A 2-ml blood sample was collected at approximately 2, 4, 24, 48, and ≥96 hours. After the last blood sample, the total blood mass of each sample was measured and the sample activity was counted in a calibrated gamma counter.

Imaging Reconstruction

The protocol for imaging reconstruction is carefully summarized in the article and is available to physicians who require these details.

Imaging Coregistration, Salivary-Gland Volume, and Isovolume ^{124}I Recovery

Images were coregistered across time by matching the transmission images at each time point with the CT portion of the PET/CT image. The resulting transformation parameters were applied to the emission image for each time point. Salivary-gland volumes were determined from the CT images. The volumes of interest were projected onto the coregistered emission image for each patient and used to determine the ratios of total activity within the gland to the gland volume, and these ratios are referred to as the image isovolume activity concentrations, which were then corrected for the most dominant partial-volume effect and the less-dominant prompt gamma coincidence effect using the ^{124}I recovery coefficients.

RESULTS

Organ Absorbed Doses per ^{131}I Activity (ODpAs) (Figure 1)

The characteristics of the patients in the nonstimulation and stimulation groups are shown in Figure 1. Within-group statistical analysis revealed no significant differences between the mean ODpAs of the submandibular and parotid glands (P>0.32). More importantly, the intergroup comparisons revealed that the ODpAs average over both gland types was reduced by 28% in the nonstimulation group (0.23 Gy/GBq) as compared with the stimulation group (0.32 Gy/GBq), which was statistically significant (P = 0.01). An even lower P value of 0.001 was obtained in an intergroup comparison of ODpA in only patients stimulated by thyroid-hormone withdrawal (eight hypothyroid patients in the stimulation group and nine in the nonstimulation group).

Lastly, separate intergroup comparisons for the parotid or submandibular glands exhibited a significant difference in ODpA between the groups for the parotid gland (P = 0.23) but not for the submandibular gland (P = 0.23) (Figure 1).

The salivary-gland absorbed dose was split into two parts: ODpA = ODpA≤24h +ODpA>24h. The first part gives the absorbed dose up to 24 hours after ^{131}I administration, and the second part is the dose absorbed between 24 and 96 hours. From the average gland ^{124}Iuptake, the ratio of the ODpA≤24h was approximately 70%.

The TSH level in the nonstimulation group was lower than the TSH level in the stimulation group (Figure 1), but this did not reach statistical significance. The relationship between ODpAs averaged over the right and left glands as a function of the TSH levels in each patient in the stimulation and nonstimulation groups were not significant.

Residence Time and Salivary-Gland Volume (Figures 2 to 4)

Figure 2 also provides the residence time and the salivary-gland-volume statistics. Within-group comparisons showed that the mean residence time was significantly different between the submandibular and the parotid glands (P<0.001), which was attributed to the difference in gland volume of the two gland types. An intergroup comparison showed that the mean residence times were about 38% lower in the nonstimulation group than in the stimulation group; the differences were not significant (P≥0.07) Moreover, no significant differences were found between salivary-gland volumes in the stimulation group and those in the nonstimulation group (P≥0.31).

The lemon-juice-induced stimulation shortly after radioiodine administration led to an overall increase in the initial uptake by the salivary glands; however, stimulation may not have accelerated the radioiodine clearance, which was almost identical to the value in the nonstimulation group. The average blood ^{124}I uptake was clearly similar in the stimulation and the nonstimulation groups. The curve-fitting parameters show that the difference in ODpA between the stimulation and nonstimulation groups was correlated with a higher extrapolated uptake value; thus, the lemon-juice-

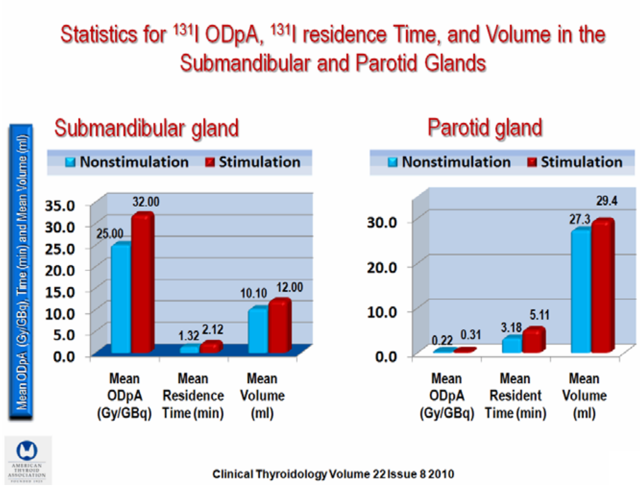
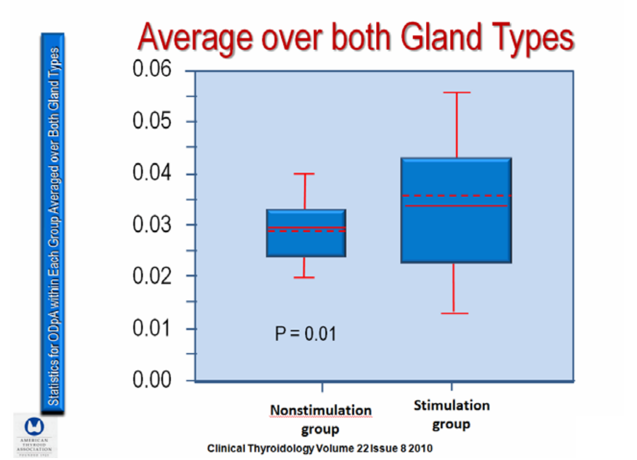


Figure 1. This figure shows the statistics for ^{131}I ODpA,^{131}I residence time in minutes and volume in milliliters. This figure is derived from data in Table 2 of Jentzen et al. ODpA = organ absorbed doses per ^{131}I activity.



Figures 2 to 4. These figures show the ODpA distributions within each group averaged for both gland types and separately for the submandibular glands and the parotid glands. The boxes represent the boundary of the 25th and 75th percentiles, and the solid lines and dashed lines indicated the median and mean values, respectively. The figures are modified from Figure 1 and 2 of Jentzen et al.

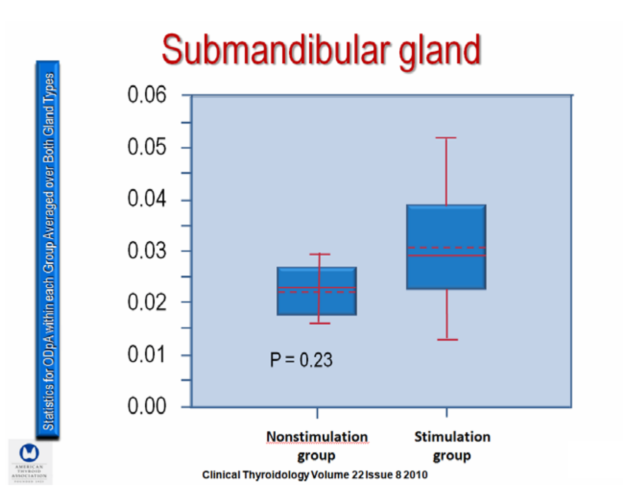


Figure 3.

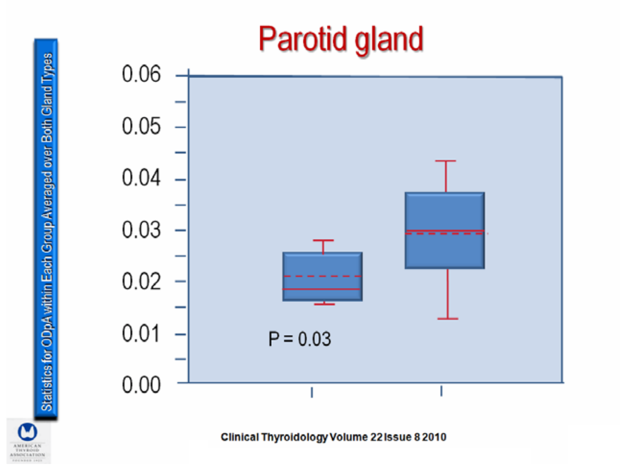


Figure 4.

induced stimulation shortly after radioiodine administration let to an overall increase in the initial uptake by the salivary glands; however, stimulation may not have accelerated the radioiodine clearance *(Figures 2 to 4)*.

CONCLUSION

This is the first prospective study to examine the influence of saliva flow stimulation on the absorbed dose to the major salivary-flow stimulation on the absorbed dose to the major salivary glands in radioiodine therapy of differentiated thyroid cancer. The use of ^{124}I PET/CT permitted an estimate of the absorbed dose in the salivary glands of patients who either chewed lemon slices (n = 10) or did not (n = 10). ^{124}I PET/CT salivary-gland dosimetry indicated that saliva flow stimulation after ^{131}I administration may increase the ODpA to salivary glands.

COMMENTARY

This is a novel study that is the first prospective study to examine the influence of stimulation of saliva flow on the absorbed radiation dose to the major salivary glands in the course of ^{131}I therapy. ^{124}I PET(CT) was used to estimate the absorbed dose in the salivary glands of patients who either did or did not chew lemon slices. There were 10 patients in each group. Contrary to the usual ^{131}I therapy protocol, the patients were not stimulated with lemon juice during the pretherapy procedure and neither ate nor drank until after completion of the last PET scan on the first day. The study showed that the mean organ absorbed doses per ^{131}I activity (ODpA) for the submandibular glands was not significantly different from that for the parotid glands. The study found that the nonstimulation group averaged over the mean ODpA in the nonstimulation group averaged over both the parotid and submandibular glands was reduced by 28% as compared with the mean ODpA in the stimulation group (P = 0.01). The mean ODpA reductions in the nonstimulation group were statistically significant for the parotid but not the submandibular glands (P = 0.23), instead showing that the ^{131}I therapy increased the absorbed doses to the salivary glands.

The authors make the point that if lemon-juice-induced stimulation during the course of ^{131}I therapy is associated with a higher ODpA, then salivary-gland dysfunction would be expected to be higher in patients in the stimulation group than those in the nonstimulation group.

In a study by Nakada et al. (1), 116 consecutive patients were asked to suck one or two lemon candies every 2 to 3 hours in the daytime of the first 5 days after ^{131}I therapy (group A). Lemon candy sucking was started within 1 hour after ^{131}I ingestion. In addition, 139 consecutive patients (group B) were asked to suck lemon candies in a manner similar to that of group A. In the group B, lemon candies were withheld until 24 hours after the ingestion of radioiodine. The onset of salivary-gland side effects was monitored during hospital admission and regular follow-up on the basis of interviews with patients, a visual analog scale, and salivary gland scintigraphy using (99m) Tc-pertechnetate. When a patient showed a persistent (>4 months) dry mouth associated with a nonfunctioning pattern on salivary-gland scintigraphy, a diagnosis of xerostomia was established. The incidence of sialadenitis, hypogeusia or taste loss, and dry mouth with or without repeated sialadenitis in group A versus group B were 63.8% versus 36.8% (P<0.001), 39.0% versus 25.6% (P<0.01), and 23.8% versus 11.2% (P<0.005), respectively. Permanent xerostomia occurred in 15 patients in group A (14.3%) and 7 patients in group B (5.6%) (P<0.05). In both groups, bilateral involvement of the parotid gland was the most frequently seen and was followed by bilateral involvement of the submandibular gland. The authors thus concluded that an early start of sucking lemon candy may induce a significant increase in salivary-gland damage.

Jentzen et al. point out that, on the one hand, sucking lemon candies increases blood flow to the salivary glands, which may lead to higher ^{131}I uptake; whereas, the increased uptake could be compensated only to some extent by increased salivary flow. This phenomenon was referred to as a rebound effect by Van Nostrand et al. (2).

Although the studies by Nakada et al. and Jentzen et al are quite different, together they reach the firm conclusion that sucking lemon sialagogues should not be done during ^{131}I therapy. Jentzen et al. suggest that further studies should focus on alternative strategies to prevent ^{131}I-induced salivary-gland damage.

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References

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