Radioiodine Uptake in Thyroid Remnants During Therapy After Tracer Dosimetry

Henry W.D. Yeung, John L. Humm, and Steven M. Larson

Nuclear Medicine Service, Memorial Sloan-Kettering Cancer Center, New York, New York

Our objective was to evaluate the effect of a diagnostic tracer dose of ^{131}I on the uptake of the therapeutic dose of ^{131}I in the ablation of a thyroid remnant or residual tumor in patients with differentiated thyroid cancer. **Methods:** Twelve consecutive patients referred for a dosimetric study and subsequent radioiodine treatment of focal neck uptake of ^{131}I were studied. The 24-h (in 1 case, 48-h) neck activity was calculated by the region-of-interest method, after both dosimetric and therapeutic administrations. The focal activity in the neck was corrected for decay and compared with the total activity administered to obtain the percentage uptake at 24 h. This procedure was performed for both the scanning dose (range, 19.8–196.1 MBq; mean, 85.1 MBq; median, 40 MBq) and the therapeutic dose (range, 1.073–5.713 GBq; mean, 2.991 GBq). The uptake of the therapeutic dose was then expressed as a percentage of the uptake of the diagnostic dose (%T/D). Counting rate linearity was established up to 350 MBq in the field of view of the γ camera used in the study. **Results:** Thirteen of a total of 16 lesions exhibited reduced uptake from the therapeutic dose, 2 remained the same, and in 1 the uptake actually increased from 0.26% to 1.01%. The %T/D ranged from 7.0% to 388.5%, with a mean of 71%. If the lesion with increased uptake is excluded, the range becomes 7.0%–102.1%, with a mean of 50%. Linear regression between the percentage uptake of the diagnostic dose to that of the therapeutic dose results in a slope of 0.42, with a correlation coefficient of only 0.75. We were unable to accurately calculate the radiation dose to the lesion from the diagnostic activity of ^{131}I, because of uncertainty about the tumor mass. **Conclusion:** The percentage uptake of the therapeutic dose is on average only one half of that predicted from the dosimetric uptake in thyroid remnants after surgery, even though the median dosimetric dose was only 40 MBq. This reduced uptake should be accounted for in the therapeutic prescription for thyroid ablation or treatment of residual thyroid cancer. We postulate that this effect is caused by radiation damage from the tracer dose during dosimetry.

Key Words: thyroid cancer; radioiodine therapy; stunning

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Before radioiodine therapy of a thyroid remnant or residual tumor after thyroidectomy, patients usually undergo dosimetry. In this procedure, a tracer dose of ^{131}I is given and the subsequent images are used to assess the presence or absence of disease. In addition, percentage uptake of iodine in the lesion is determined using both γ camera images and a neck probe. This information is used to estimate the amount of therapeutic radioiodine required to achieve an adequate radiation absorbed dose to the lesion. This procedure is based on the assumption that the therapeutic dose has pharmacokinetics identical to those of the tracer dose.

In the past, activities as high as 370 MBq (10 mCi) were administered as the tracer dose, on the basis of the observation that higher activities result in visualization of more lesions and better disease staging (*1,2*). However, several authors have produced evidence suggesting different kinetics after the therapeutic and diagnostic doses (*3–7*). Specifically, neck uptake on the post-therapy image appeared significantly less than that on the diagnostic image for some patients. This finding raised concern that the higher tracer dose would actually reduce iodine trapping of the subsequent therapeutic dose by the thyroid remnant or tumor, thus compromising the effect of the larger therapeutic dose. In a recent publication, Park et al. (*8*) reported a statistically significant lower success rate of thyroid remnant ablation using 111–370 MBq (3–10 mCi) ^{131}I as the diagnostic dose, compared with 11 MBq (300 μCi) ^{123}I. Kim et al. (*9*) also reported a lower percentage of successful ablation after a scanning dose of 370 MBq, compared with 37 or 185 MBq. This effect has been called thyroid stunning and is the main reason that lower tracer doses are now used (*10–12*).

However, reports of stunning have been mostly anecdotal, based on the appearance of the diagnostic and post-therapy images, which can be subject to error because of the large difference in counting rate and the difference in timing after dose administration. Definite measured evidence is lacking. Controversy remains about whether thyroid stunning is a real phenomenon and, if so, when the tracer dose is too high.

In this study, we addressed these questions by quantitatively evaluating uptake of both the diagnostic tracer dose of ^{131}I and the therapeutic dose in the ablation of thyroid remnants or residual tumors in patients with differentiated thyroid cancer.

MATERIALS AND METHODS

Twelve consecutive patients with focal neck uptake after a dosimetric study were re-evaluated after subsequent radioiodine treatment. The 24-h (in one case, 48-h) neck activity was calculated by the region-of-interest (ROI) method, after both dosimetric and

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For correspondence or reprints contact: Henry W.D. Yeung, MD, Nuclear Medicine Service, Memorial Sloan-Kettering Cancer Center, 1275 York Ave., New York, NY 10021.

therapeutic administrations. Counts in tumor ROIs were corrected for background activity using peritumor regions of the same area and then converted to activity using counts obtained from a ^{131}I standard placed on the camera either during or after patient scanning. The focal activity in the neck was corrected for decay and compared with the total activity administered to obtain the percentage uptake at 24 h. This procedure was performed after both the tracer and the therapeutic administration. The uptake after therapy was then expressed as a percentage of the uptake of the diagnostic dose (%T/D). All patients were studied in a hypothyroid state with serum TSH levels greater than 30 and were kept on a low-iodine diet. The treatment doses were all given on day 8 after the tracer doses, with the patients kept under the same conditions.

To ensure that the reduction in lesion uptake after therapeutic doses was not a consequence of increased camera dead-time, the counting rate linearity of the instrument was measured for the range of radioactivity encountered. Syringes containing different activities, up to 350 MBq, of ^{131}I were imaged on the same γ camera (Vertex; ADAC Laboratories, Milpitas, CA) as that used for patient studies, with a 1.588-cm (0.625-in.) sodium iodide crystal and a high-energy, high-resolution collimator.

RESULTS

The counting rate linearity of the γ camera was confirmed with a least squares fit of the counting rate-versus-activity curve (Fig. 1). The regression r^2 coefficient was 0.9998 over a range from 0 to 350 MBq.

Twelve patients were studied, with the diagnostic dose ranging from 19.8 to 196.1 MBq (mean, 86.5 MBq) and the therapeutic dose ranging from 1.073 to 5.713 GBq (mean, 3.027 GBq). Four patients had 2 lesions seen on the neck image, and the uptakes of the individual lesions were computed separately.

As shown in Table 1, percentage uptake of the tracer dose ranged from 0.13% to 29.80% (median, 1.45%), whereas that of the therapeutic dose ranged from 0.01% to 28.80% (median, 0.67%). The %T/D, on a patient-to-patient basis, ranged from 7.0% to 102.1%, with a median of 55% and a mean of 50%. In other words, the percentage uptake of the therapeutic dose was, on average, only half that predicted by the diagnostic or tracer dose. This finding was true even for tracer doses as low as 74 MBq (2 mCi) or less (patients 1, 2, 5–8, and 12).

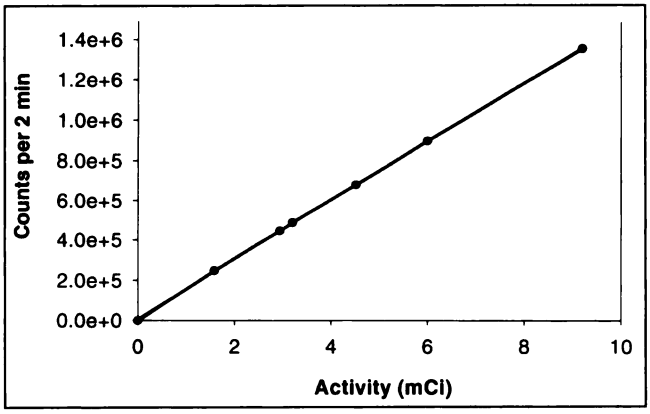

FIGURE 1. Linearity of γ camera versus activity of ^{131}I (r^2 = 0.9998).

TABLE 1
Percentage Uptake of Diagnostic Dose, Percentage Uptake of Therapy Dose, and %T/D

Patient no.	Diagnosis Dose (MBq)	Diagnosis Percentage uptake	Therapy Dose (GBq)	Therapy Percentage uptake	%T/D
1	40.7	29.80	1.891	28.80	96.6
2*	40.7	18.95	2.960	10.90	57.5
		1.48		0.73	49.3
3	196.1	0.15	5.713	0.15	102.1
4	78.8	1.46	3.774	0.78	53.4
5	37.0	0.24	5.550	0.18	75.0
6*	37.0	7.25	2.775	4.07	56.1
		1.00		0.32	32.0
7	37.0	2.23	1.106	0.38	17.0
8*	69.9	1.10	2.960	0.62	56.4
		0.17		0.09	53.5
9	188.7	1.40	2.997	0.10	7.0
10*	96.2	10.90	2.757	2.54	23.3
		0.26		1.01	388.5
11	196.1	0.13	1.073	0.01	10.0
12	19.8	9.70	2.775	6.10	62.9

*Two lesions were identified in this patient.

On a lesion-by-lesion basis, the %T/D ranged from 7.0% to 388.5%, with a median of 55% and a mean of 71%. The only lesion that showed significantly increased percentage uptake of the therapeutic dose compared with the tracer percentage uptake (0.26%–1.01%) occurred in patient 10, for whose other lesion percentage uptake actually dropped from 10.9% for the tracer dose to 2.54% for the therapeutic dose. For this patient, the total uptake of the therapeutic dose was still significantly less than that of the tracer dose. The reason for the increased percentage uptake of the therapeutic dose for this 1 lesion is not known. The increase may be a consequence of radiation response for the more iodine-avid lesion, which acts as a sink for the ^{131}I in the tracer dose, thus allowing the less avid lesion to accumulate more ^{131}I from the therapeutic dose.

When the percentage uptake of the therapeutic dose was plotted against that of the diagnostic dose (Fig. 2), the correlation coefficient was only 0.75, suggesting a poor correlation between diagnostic uptake and therapeutic uptake in this cohort of patients. The plot of %T/D versus tracer dose showed wide scatter, with no correlation between the diagnostic dose and the %T/D (Fig. 3).

DISCUSSION

As shown in this study, the reduction in uptake of the therapeutic dose did not appear to correlate with the magnitude of the tracer activity administered for dosimetry. Ten of the 12 patients studied showed therapeutic uptake less than 90% of tracer uptake. Seven patients who had tracer activities of less than 74 MBq (2 mCi) had an average %T/D

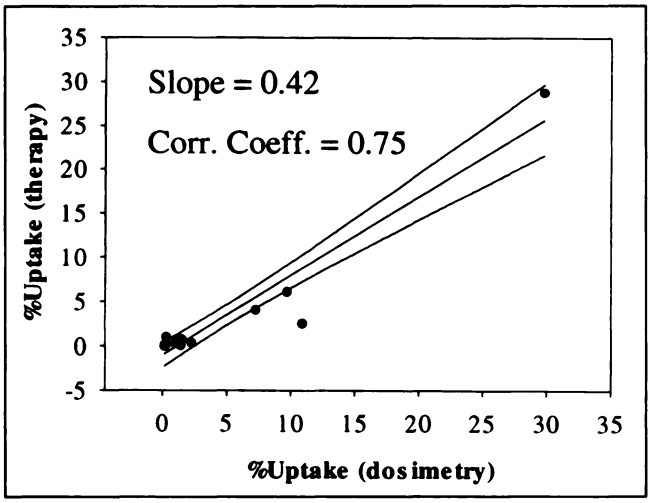

FIGURE 2. Percentage uptake of diagnostic dose versus therapeutic dose. Corr. Coeff. = correlation coefficient.

of 57%, compared with 40% for the 5 patients who had tracer activities of 74–185 MBq (2–5 mCi). Only 2 patients had therapeutic uptake similar to tracer uptake, with %T/Ds of 96.6% and 102.1%, and 1 of these received 196.1 MBq (5.3 mCi), the highest tracer activity given in this group of patients.

Kao and Yen (*13*) reported that 73.5% of 468 patients had scintigraphic patterns of apparently lower uptake on post-therapy scans than on diagnostic scans, using 111 MBq (3 mCi) ^{131}I. McDougall (*10*), however, using 74 MBq (2 mCi) as the tracer, reported only a 1.4% incidence of visually decreased uptake on the post-therapy image and concluded that a dose of 74 MBq seldom interferes with subsequent therapy. This finding disagrees with our experience with direct measurement of uptake after therapy, probably because of the difference in methodology. Direct measurement of uptake can pick up small differences that may look the same on the images.

Conceptually, one might expect that the %T/D should correlate well with the radiation dose delivered by the tracer,

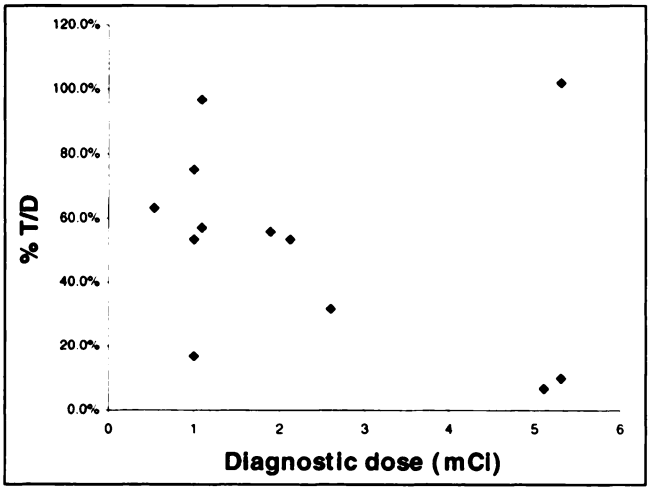

FIGURE 3. %T/D versus diagnostic dose.

which would depend both on the uptake of the administered activity and on the tissue mass. Unfortunately, the actual radiation dose delivered is not known, because the mass of the residual tumor or thyroid tissue is difficult to measure, especially when it is too small to be visualized on anatomic imaging such as sonography, CT, or MRI. When the uptake is low, the tissue mass is probably also very low, so the radiation dose delivered per unit activity of radioiodine can be high enough to suppress the subsequent therapeutic dose. Assuming uptake of 0.37 MBq (0.01 mCi), i.e., 0.5% of a 74-MBq (2-mCi) tracer activity, the radiation dose could be as high as 30 Gy for a 0.1-g thyroid lesion or 3 Gy for a 1-g thyroid lesion.

By direct measurement, we found that the average uptake of the therapeutic dose was only 50% of that predicted by the tracer dose. However, wide variation exists, with a range of 7.0%–102.1%. In effect, the tracer dose uptake can be used to predict only the upper limit of the therapeutic uptake. The %T/D (or the degree of stunning) is not predictable.

One possible source of error in our measurement is camera dead-time at the high counting rate during post-therapy imaging. In this study, the camera used was shown to exhibit a linear counting rate response up to 350 MBq (9.5 mCi), when all our patients had activity less than 370 MBq in the neck region at the time of the measurement. In fact, the patient who had the highest activity in the thyroid remnant on the post-therapy scan (patient 1) had no stunning as measured by this method, with a %T/D of 96.6%.

Another possible source of error is the delineation of the tumor and the background ROI on the images. However, because we used the same ROI for both the diagnostic and the post-therapy images and subtracted the counts of the background ROI with the same area adjacent to the tumor, the errors cancel each other when the count ratios are computed.

We have also tested the reproducibility of patient uptake measurements on the γ camera. One potential source of variation is counting statistics, i.e., the variability in counts from a fixed activity that is repeatedly measured. We did not reposition and recount the patients in this study. However, we verified that the variation in counts from repeated measurements of a standard obeys Poisson statistics: the error in counts is given by the square root of the total number of counts within the ROI. The total number of counts within the regions drawn around the lesions within this study ranged from 2,849,775 (patient 1) to 3,739 (patient 11). The percentage error corresponding to 1 SD from remeasurement therefore ranges from 0.06% (patient 1) to 1.6% (patient 11). Neck attenuation was assumed not to vary during the week between the dosimetric and the therapeutic treatments.

A second potential source of variation is accuracy in ROI placement. The ROI for each patient was drawn generously, i.e., with a 3- to 4-pixel berth around the intense thyroid region. This region was copied (to preserve the pixel number) to an area adjacent to the thyroid for background subtraction. Therefore, the uptake values were corrected for background activity from the blood and other tissues within

the neck. The data from all patients were reanalyzed using 3 ROIs to determine the sensitivity of the analysis to ROI selection. For example, the background-corrected counts within the hottest lesion (patient 1 post-therapy) were 2,849776, 2,833,301, and 2,832,547, yielding a percentage SD of 0.343%. For the lowest uptake (patient 11), these ROI numbers were 3896, 3862, and 3739, yielding a percentage SD of 2.155%.

The root sum of squares of the combined error for the patient with the lowest uptake was 2.68%. This error was considerably smaller than the magnitude of the changes observed between the dosimetric and the therapeutic scans. For most lesions, the combined percentage error was less than 1%.

In a paired Student *t* test applied to the patients, the data pairs corresponded to uptake after dosimetry and therapy. The results of this test for 15 lesions yielded a *t* statistic of 2.453681, which yielded a *P* of 0.013923. The finding that the therapeutic uptake was less than the dosimetric uptake was highly significant.

Rini et al. (*14*) suggested that the bioavailability of ^{131}I in capsule form may be a source of error in the calculation of percentage uptake of radioiodine. In our patients, all diagnostic and therapeutic radioiodine was given orally in liquid form.

CONCLUSION

We have shown that uptake of the therapeutic dose by neck lesions was significantly less than that predicted by the diagnostic dose of ^{131}I in most patients. On average, the therapeutic dose uptake was only 50% of the diagnostic dose uptake. This so-called stunning effect was present even for diagnostic doses as low as 37.0 or 74 MBq (1 or 2 mCi).

The stunning effect affects patient management in multiple ways. If dosimetry is performed, allowance should be made for stunning when calculating the therapeutic dose. Alternatively, ^{123}I, which theoretically has a lower radiation dose than ^{131}I, can be used as the tracer dose. For post-thyroidectomy patients, $^{99m}TcO_4$ can be used for assessing the necessity of ablation. If other clinical considerations mandate ^{131}I treatment, e.g., a rising thyroglobulin level, one should consider giving ^{131}I therapy without obtaining a diagnostic image. If calculation of body and blood clearance is desired, a true tracer dose of less than 3.7 MBq (0.1 mCi) can be used instead of the 74–185 MBq (2–5 mCi) normally required for imaging.

What is not known is whether stunning can be extrapolated to metastatic lesions in the rest of the body and whether stunning is an actual treatment effect of the tracer dose, i.e., a permanent effect, or just a temporary effect. Also, the cause of stunning is not yet understood. One hypothesis is that the radiation dose delivered by the tracer ^{131}I administration destroys the follicular histology that concentrates radioiodine in the remnant. The variable level of differentiation can then explain differences in the level of stunning. A second hypothesis is an alteration in the level of expression of the iodine symport mechanism caused by radiation damage to the thyroid cells. Further work is required to elucidate the mechanism.

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