# Prolonged Iodine Clearance with a Depletion Regimen for Thyroid Carcinoma: Concise Communication

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**Prior studies suggested iodine depletion as a means of enhancing radioiodine uptake into metastases from well-differentiated thyroid cancer. Data are not available regarding the secondary effects of this maneuver on iodine clearance and on total-body radiation. Accordingly we have measured inorganic iodine clearance, total body iodine, tumor and total-body retention of radioactive iodine before and during a diet-and-diuretic regimen designed to induce iodine depletion. Total-body iodine decreased by 25% to 66% ($p < 0.05$). The amount of radioiodine taken up and retained by tumor tissue increased 146% (range 48–243%) following the depletion regimen in three studies (two patients). However, because the iodine clearance decreased by 56% (range 40–71%), the total-body radiation per standard 150-mCi dose increased by 68% (range 19–111%). Consequently, the increase in lesion irradiation relative to the increment delivered to the total body was only 46% (range 24–82%). We conclude that iodine-depletion regimens are less effective than prior studies suggest.**

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Total thyroidectomy is the initial treatment usually chosen for patients with well-differentiated thyroid carcinoma. Following surgery, residual tumor in the neck can frequently be demonstrated by radioiodine imaging. In patients with residual disease, large doses of iodine-131 ablate tumor tissue in the majority of patients but not in all. Several known biologic phenomena limit the efficacy of radioiodine therapy for treatment of this tumor. The iodine-concentrating capacity of the cancer tissue is poor relative to normal thyroid cells (*1*). The cumulative effect of total-body radiation on the hematopoietic system limits the total amount of therapy that can be given to an individual patient (*2*). To maximize the uptake of radioiodine by residual thyroid cancer, a standard technique is to withhold thyroid replacement, thus increasing endogenous TSH stimulation of residual tissue (*2*). An additional method, acute iodine depletion, has been suggested as a means of further enhancing cancer tissue uptake of I-131. To date, iodine-depletion regimens (IDR) have included a low-iodine diet (LID) in conjunction with iodine diuresis caused by mannitol, ethacrynic acid, or lasix (*3–6*). Although total-body iodine has not been measured during these regimens, a two- to threefold increase in I-131 uptake has been demonstrated (*3–6*).

Recently, Beyer et al. demonstrated that hydrochlorathiazide is a potent stimulator of renal iodine clearance in the dog (*7*). Stimulated by this observation, we studied hydrochlorathiazide as a component of the previously proposed iodine-depletion regimen. Measurements of total-body iodine documented its efficacy in producing iodine depletion in conjunction with diet. More importantly, however, our observations indicated that the regimen results in prolonged serum disappearance and reduced renal clearance of radioiodine. As a result, the IDR increases total-body radiation for a given dose of

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**TABLE 1. CLINICAL CHARACTERISTICS OF PATIENTS**

| Study | Age/Sex | Pathology | Site of metastasis | Prior I-131 | Diuretic | TSH* (μU/ml) |
|---|---|---|---|---|---|---|
| 1A | 66 F | Pap-fol | Femur | 465 mCi | HCTZ | >50 |
| 1B | 66 F | Pap-fol | Femur | 625 mCi | Lasix | >50 |
| 2 | 31 F | Pap-fol | Neck | 200 mCi | HCTZ | >50 |
| 3 | 33 F | Pap-fol | Neck | 417 mCi | HCTZ | 24.3 |

* TSH obtained before iodine-depletion regimen.

I-131. The real therapeutic benefit of this method is therefore significantly less than has been suggested by previous studies.

## METHODS

**Patients.** Four studies were conducted after total thyroidectomy in three patients (Table 1) with well-differentiated thyroid carcinoma and residual functioning metastases. All patients were withdrawn from tri-iodothyronine suppression 1 mo before the study period. Initial TSH levels were measured and found elevated (Table 1). Sequential TSH concentrations were not obtained, since I-131 uptake into thyroid cancer tissue stabilizes 2 wk after tri-iodothyronine withdrawal and no further increase occurs between 2 and 3 wk (*8*). Patients were hospitalized during these studies and their diet controlled by a clinical nutritionist.

**Protocol.** This included three 5-day periods: before, during, and after an iodine-depletion regimen (IDR). Measurements of iodine kinetics were made during the first and final 5-day periods. The IDR consisted of a low-iodine diet (*4*); hydrochlorothiazide, 100 mg b.i.d., or furosimide, 40 mg b.i.d. (one study); sodium chloride, 12 g, and 3 liters of water, daily for 5 days. The low-iodine diet used is designed to provide <25 μg of iodine daily (*4*). Daily weights or intake and output determinations were obtained to document adequate hydration. Each patient received a standard 150-mCi treatment dose of radioiodine.

**Methods.** Lesion uptakes, serum half-time, and volumes of distribution of I-131 were determined first after a 5-mCi tracer dose. The volume of distribution was determined according to the method of Brownell (*9*). Serum inorganic iodine was determined in 2-ml samples with an assay sensitivity of 0.2 μg/100 ml. The serum inorganic iodine was determined on samples obtained by pooling equal volumes of six or more specimens from the 48-hr period before and immediately after the IRD. Serum and urinary I-131 concentrations were determined by gamma spectrometry. Plasma samples were counted after precipitation with trichloroacetic acid to eliminate protein-bound I-131. The total-body iodine was calculated as the product of the volume of distribution and the serum inorganic iodine concentration. Renal clearance was calculated by the formula C = UV/P, where urine and plasma determinations represent I-131 cpm. A minimum of four sequential urine specimens of 24 hr each were counted in each subject before and after the IDR. Data are represented for each subject as the means of these determinations.

Lesion uptake was estimated serially over a 10-day period following administration of an imaging dose of 5 mCi. The activity in the lesion was determined using a camera system with a parallel-hole collimator and a

**TABLE 2. EFFECT OF IODINE-DEPLETION REGIMEN ON INORGANIC IODINE MASS**

| | Plasma inorganic iodine (μg/100 ml) | | | Volume of distribution of iodine (liters) | | | Total-body iodine (μg) | | |
|---|---|---|---|---|---|---|---|---|---|
| Study | Pre* | Post† | Change (%) | Pre | Post | Change (%) | Pre | Post | Change (%) |
| 1A | 0.5 | 0.4 | −20.0 | 29.6 | 24.7 | −16.6 | 148 | 98.8 | −33.2 |
| 1B | 1.1 | 1.0 | −9.1 | 26.5 | 21.9 | −17.4 | 291.5 | 219.0 | −24.9 |
| 2 | 0.9 | 0.4 | −55.6 | 31.5 | 24.1 | −23.5 | 283.5 | 96.4 | −66.0 |
| 3 | 1.1 | 0.8 | −27.3 | 22.5 | 18.1 | −19.6 | 247.5 | 144.8 | −41.5 |

* Before iodine-depletion regimen.
† After iodine-depletion regimen.

**TABLE 3. EFFECT OF IODINE-DEPLETION REGIMEN ON INORGANIC IODINE CLEARANCE**

| Study | Renal iodine clearance (ml/min) Pre* | Post† | Change (%) | Signif-icance‡ | Serum half-time (hr) Pre* | Post† | Change (%) | Signif-icance§ |
|---|---|---|---|---|---|---|---|---|
| 1A | 20.0 | 10.2 | −49 | p <0.001 | 18 | 27 | +50 | p <0.001 |
| 1B | 7.6 | 2.2 | −71 | p <0.001 | 35 | 74 | +111.4 | p <0.001 |
| 2 | 34.0 | 12.5 | −63.2 | p <0.001 | 11 | 20 | +81.8 | p <0.001 |
| 3 | 15.7 | 9.3 | −40.8 | p <0.05 | 16 | 19 | +18.8 | p <0.001 |

* Before iodine-depletion regimen.
† After iodine-depletion regimen.
‡ Significance determined by unpaired t-test. N = 4 or 5 for each determination.
§ Significance determined by t-test on the slopes of regression line. N > 14 for all determinations.

computer to integrate the total counts in the region of interest. The actual microcurie activity in the lesion was determined by comparison of lesion counts with those from a known amount of radioactivity in a tissue-equivalent phantom. The I-131 standard source used in the phantom was analyzed daily and cross-checked using computer calculations of radioactive decay. Computer determinations agreed well with actual counts provided by the camera system.

**Calculations.** The results obtained from the above procedures were subjected to linear regression analysis using the natural logarithms of the plasma activity against time. This permitted determination of effective half-time of the radioactivity within the plasma. All linear regressions had correlation coefficients >0.98. The s.e.m. for estimates of slopes ranged from 1.8% to 4.9% of the slope estimates.

In two patients, lesion doses were calculated in terms of $\mu$Ci/day, since it was impossible to estimate lesion mass. Since lesion masses were assumed to be the same during each scanning procedure, the ratio between microcurie-days of exposure in each case would be the same as the ratio between rad doses.

In the case of Patient 1, the tumor doses (in rad) were calculated after review of radiographs and determination of lesion size by analysis of AP and lateral films of a lytic thigh lesion. Dose calculations assumed that uniform distribution of I-131 existed within the tumor, that beta emission was totally absorbed by the tumor, and that 35% of the photons that originated in the tumor were absorbed by the tumor. Percent increase (%) in lesion dose relative to increase in total-body dose was calculated by the formula:

$$\%\ \text{increase} = \frac{\%\ \text{increase LR} - \%\ \text{increase TBR}}{100\% + \%\ \text{increase TBR}}, \quad (1)$$

where LR = lesion radiation, and TBR = total-body radiation.

RESULTS

In all four studies, the iodine-depletion regimen (IDR) resulted in a decrease in the serum iodine, with a mean decrement of 28%. Because of the variability in single measurements, these changes were not statistically significant. On the other hand, the volume of iodine distribution decreased significantly by 16.6 to 23.5%, and the total-body iodine by 24.9% to 66% (Table 2).

In all four individual studies, the IDR resulted in a decrease in the serum half-time of inorganic radioiodine (Table 3, Fig. 1) with changes ranging from 18.8 to

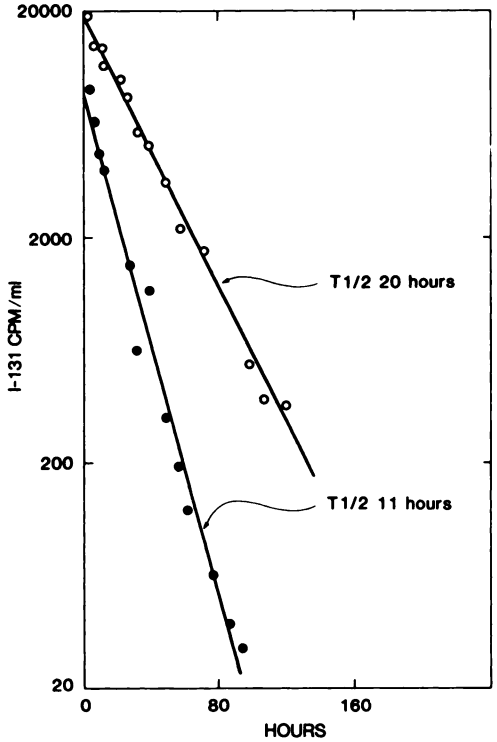


**FIG. 1.** Log-linear disappearance of nonprotein-bound $^{131}$I from plasma in single patient (Study 2) before (closed circles) and after (open circles) iodine-depletion regimen induced by diet and diuretics. $T_{1/2}$ equals half-time of disappearance of inorganic iodine.

**TABLE 4. EFFECT OF IODINE-DEPLETION REGIMEN ON RADIATION EXPOSURE**

| Study | Total-body abs. dose (rad) | | | Lesion radiation (μCi-days) | | | % Increase in lesion relative to total-body increase (%) |
|---|---|---|---|---|---|---|---|
| | Pre | Post | % Increase | Pre | Post | % Increase | |
| 1A | 1.05 | 1.67 | 59 | 443 (12.7)† | 924 (26.6) | 108 | 31 |
| 1B | 2.49 | 5.26 | 111 | 213 (6.1) | 815 (23.5) | 283 | 82 |
| 2 | 1.12 | 2.04 | 82 | * | — | — | — |
| 3 | 1.57 | 1.87 | 19 | 51.3 | 76 | 48 | 24 |
| Mean | 1.56 | 2.71 | 68 | 236 | 605 | 146% | 46% |

* Unable to measure lesion uptake.

† Rad to lesion are indicated in parentheses.

111.4% ($p < 0.001$ for all). This resulted from decrements in the renal iodine clearance, as determined by radiokinetic measurements. Each subject exhibited decreased renal clearance ranging from −40.8% ($p < 0.05$) to −71% ($p < 0.001$).

The observed decrease in plasma and renal clearances of radioactive iodine during the IDR resulted in a mean increase of 68% in total-body radiation (range 19–111%, Table 4) from the standard 150-mCi dose. In three of four studies, the uptake of radioiodine by the functioning metastases was sufficient to determine the lesions' dose of radiation before and after the IDR. The lesion radiation increased in all three studies, with a mean increase of 146% (range: 48–283%). However, when corrected for the increase in total-body radiation, the increase in lesion radiation, relative to the rise in total-body irradiation, was only 46% (range: 24–82%, Table 4).

## DISCUSSION

This and prior studies demonstrate that an iodine-depletion regimen can significantly increase uptake into metastatic lesions of well-differentiated thyroid carcinoma. Before assuming that this effect will be beneficial, however, one must demonstrate that total-body radiation has not increased proportionately to the increase in lesion uptake. Unexpectedly, we found a marked decrease in iodine clearance in each patient studied following iodine depletion. This effect, which resulted in an increase in total-body absorbed dose, partially but not completely offset the beneficial action on tumor uptake. Thus, while lesion uptake increased 146%—an amount similar to that found by Hamburger et al. (*4*)—this represented only a 46% gain relative to the total-body dose. Our data indicate that changes in plasma iodine clearance must be taken into account when assessing the role of total-body iodine depletion, and questions arise regarding the use of IDR without prior study of iodine kinetics in individual patients.

Previous major studies of iodine depletion were conducted by Hamburger et al. (*4,5*). They observed that acute iodine depletion, with a low-iodine diet and diuresis, resulted in a two- to threefold increase in lesion radioiodine uptake in 16 of 25 patients with inoperable, well-differentiated thyroid carcinoma. This increase has been thought to result from: first, the observed decrease in serum and total-body I-127 results in an increased ratio of I-131 to I-127 presented to the lesion; second acute iodine depletion may result in an intrinsic (not TSH-mediated) increase in iodine uptake by functioning thyroid tissue (*6*). Our study reveals a possible third mechanism, decreased renal I-131 clearance, which resulted from diet- and diuretic-induced iodine depletion. This 65% prolongation in serum half-time would also partially explain the increase in lesion uptake. This phenomenon was observed following the use of both hydrochlorothiazide and lasix.

The cause of the observed decrease in renal I-131 clearance following diuretic-induced iodine depletion has not been clearly established. The following considerations suggest that sodium and consequently volume depletion may have been a factor. Bricker (*10*) demonstrated that glomerular filtration is the major determinant of renal iodine clearance. In addition, the renal excretion of both iodide and chloride are sodium-dependent. The renal iodide/sodium excretion slope is less steep than that for chloride/sodium. Consequently, states of sodium depletion enhance the relative rate of iodide reabsorption by the kidney (*7*). We observed a 19% decrease in the volume of distribution of radioactive iodine at the end of the iodine-depletion regimen. Presumably the volume of distribution is equivalent to the extracellular volume. The high oral sodium chloride intake (12 g/day) routinely resulted in nausea and/or

diarrhea. Therefore, our subjects may have been volume-depleted and, as a consequence, had a reduction of renal iodine excretion. In a study with euthyroid subjects, Barakot (*6*) did not observe a decrease in renal I-131 clearance following diuresis induced by i.v. mannitol and 4 l of saline. This regimen would tend to result in volume expansion rather than volume depletion. Taken together, these data suggested that the regimen we described should be reexamined with the addition of volume expansion shortly after the I-131 therapy dose has been administered.

The necessity of adding diuretics to a saline diuresis for achievement of iodine depletion in the thyroidectomized patients is by no means clear. Goslings (*5*) found no difference in the rapidity or magnitude of iodine depletion in seven patients treated with a low-iodine diet alone, in comparison with another seven given a low-iodine diet and ethacrinic acid. Furthermore, he noted a mean 179% increase in tumor I-131 uptake after the low-iodine diet alone (5 days). This improvement in tumor I-131 uptake is comparable to that noted both in our study and that of Hamburger (*3*,*4*), which used the more complicated regimen including diuretics.

Diuretic-mediated iodine-depletion regimens have several disadvantages. They are not universally successful, and only 15 of 25 patients studied by Hamburger (*4*) experienced substantial improvement in the lesion uptake of I-131. Furthermore, the regimens are complex and require hospitalization to ensure medication compliance and fluid balance. These factors, in addition to our observations noted above, question the general clinical utility of diuretic-mediated iodine-depletion regimens.

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