Four- to Twenty-four-Hour Uptake Ratio: An Index of Rapid Iodine-131 Turnover in Hyperthyroidism

Recal Akty, Karim Rezai, James E. Seabold, Robert S. Bar and Peter T. Kirchner

Departments of Radiology and Internal Medicine, The University of Iowa College of Medicine, Iowa City, Iowa

Rapid thyroidal iodine turnover may contribute to 131I therapy failure in patients with hyperthyroidism. The utility of a 4- to 24-hr 131I uptake ratio was evaluated as an index of thyroidal iodide retention in hyperthyroid patients. Methods: In 433 hyperthyroid patients, the success of 131I therapy was correlated with the following factors: gender, pretreatment with antithyroid drugs, clinical diagnosis, magnitude of early and late thyroidal 131I uptake values, and the 4- to 24-hr 131I uptake ratio. Results: Of the 433 patients, 362 patients (84%) had a successful outcome after a single therapeutic dose of 131I while 71 (16%) did not. Multiple linear regression analysis revealed that the highest statistically significant predictor of outcome was the 4- to 24-hr 131I uptake ratio (p-value < 0.001); all other factors showed a weaker association. An 131I uptake ratio of > 1 was found in 67 (15%) patients. Thirty-two of these 67 patients (48%) failed 131I therapy, whereas those patients with uptake ratios of < 1.0, only 39/366 (11%) failed 131I therapy. Conclusion: The 4- to 24-hr 131I thyroidal uptake ratio is a practical substitute for exact determination of the effective half-life. It identifies patients who are likely to have a rapid 131I turnover without the need for extended thyroid uptake measurements. An 131I uptake ratio of ≥1 was found in 15% of hyperthyroid patients and was associated with a near 50% 131I therapy failure rate.

Key Words: hyperthyroidism; rapid thyroidal iodine-131 turnover; Graves' disease

dose administered (2.4–9). Other factors, including thyroid size, gland uniformity and pretreatment with antithyroid drugs, also affect therapeutic outcome (2.5–11).

The radiation dose delivered to the thyroid gland depends on the concentration of 131I per gram of thyroid tissue as well as the residence time of 131I in the thyroid gland. The latter is generally not measured. The mean biologic half-life is variable and is often assumed to be 24 days, which is equivalent to an effective half-life of 6 days (2.9). A significant number of hyperthyroid patients, however, may have rapid thyroidal 131I turnover resulting in a shortened residence time of 131I in the thyroid gland (2.9–11). Rapid thyroidal 131I turnover is clinically significant in two respects: (a) it decreases the radiation dose delivered to the gland, which is a potential cause for therapeutic failure; and (b) it increases the whole-body radiation dose secondary to the additional release of protein-bound 131I into the vascular system (2.10).

The effective half-life of 131I can be measured by sequential thyroid uptake determinations over a period of 5–7 days (2.9,10). This approach, however, is time-consuming and not extremely practical in most clinical settings. We have utilized an alternative approach to obtain an index of thyroidal 131I turnover in hyperthyroid patients by comparing the pretherapy 4–6 hr 131I uptake values to 20–25 hr 131I uptake values and correlating this uptake ratio to therapeutic outcome.

MATERIALS AND METHODS

Patients

There were 370 women and 90 men (mean age 40 ± 17 yr) included in this study. The medical records of all hyperthyroid patients referred to the nuclear medicine division at our institution for 131I therapy between July 1980 and August 1993 were reviewed. A complete set of early (4 to 6 hr) and late (20 to 25 hr) 131I uptake measurements was available in 460 of 525 patients, who subsequently received 131I therapy for hyperthyroidism. A total of 402 patients had the clinical diagnosis of Graves’ disease, and 58 patients had other etiologies for hyperthyroidism. The diagnosis of Graves’ disease was primarily based on the finding of a uniformly enlarged thyroid gland in conjunction with a suppressed serum thyroid stimulating hormone (TSH) level (<0.1). The non-Graves’ group included 37 patients with multinodular goiter, 12 with superimposed Graves’ disease, 4 with Hashimoto’s thyroiditis, 2 with Plummer’s disease and 3 with autonomous hyperfunctioning nodules.

All patients were evaluated by an endocrinologist and had thyroid function tests, including TSH, free thyroxine and total thyroxine levels. Serum triiodothyronine levels, thyroid-stimulating immunoglobulin assay and thyroid scans were also obtained in several patients. All medications that could interfere with thyroidal 131I uptake were stopped 4 to 6 days before 131I uptake measurements and/or 131I therapy. Iodine-131 uptake measurements were obtained 4–6 and 20–25 hr after oral administration of 3–9 μCi of sodium iodide (131I) using a single-channel analyzer spectrometer. All measurements were obtained with the uptake probe centered on the thyroid cartilage at a distance of 25 cm. A standard 131I source was also counted in a Picker nuclear neck phantom at the same distance. Thyroidal uptake was calculated according to the following equation: percent 131I uptake = (neck counts – thigh counts) × 100/(standard counts – background counts).

Each patient was evaluated by an experienced nuclear medicine physician who estimated the gland weight by thyroid palpation. The estimated thyroid gland weight was recorded in the chart at the time of therapy in 320 patients; it was not recorded in the remaining cases. The therapeutic dose of 131I was based on the targeted dose of 0.1–0.15 mCi/g of thyroid. A dose of 0.15 mCi of 131I per gram of tissue was used for patients over 50 yr of age as well as those with nodular and/or very large thyroid glands.

Iodine-131 therapy outcome was assessed from the patient’s clinical follow-up and was classified as successful if at least one of the following criteria was met: (a) development of clinical symptoms of hypothyroidism or (b) elevation of serum TSH to normal or above normal levels. The 131I therapeutic outcome was classified as unsuccessful if the patient had: (a) persistent clinical or biochemical hyperthyroidism and needed antithyroid medication or (b) required additional 131I therapy or surgical treatment for persistent hyperthyroidism lasting an average of 5.2 mo after an initial therapeutic dose of 131I. Twenty-seven patients were lost to follow-up after the initial 131I therapy. Therefore, outcome data were available for 433 patients. The mean follow-up period was 26 mo (range 6–141 mo). Early peaking of 131I uptake in the thyroid gland was defined as an early (4 to 6 hr)/late (20 to 25 hr) 131I uptake ratio of ≥1.0.

Statistical Analysis

Parameters in the two groups of patients with successful and unsuccessful 131I therapeutic outcomes were compared using two-tailed Student’s t-test and z-test. A p-value of < 0.05 or z-values of > 1.96 or < -1.96 were considered significant. Multiple linear regression analysis was performed to test if the outcome of 131I therapy correlated with the following independent factors: age, sex, estimated weight of the gland, therapy dose, magnitude of early and late 131I uptake values, clinical diagnosis, T4 and FT4 levels, early-to-late 131I uptake ratio and pretreatment with antithyroid medications. Binary values were assigned to nonparametric variables, including sex, diagnosis and therapy outcome.

RESULTS

Of 433 evaluable patients, 362 (83.6%) had a successful outcome after one therapeutic dose of 131I. Of these 362 patients, 322 had Graves’ and 40 had non-Graves’ disease. The administered treatment dose of 131I was 145 ± 93 μCi per estimated gram of tissue. One-hundred thirty patients (36%) were treated with antithyroid medications before 131I therapy; the remaining 232 patients received no antithyroid medications before 131I therapy (Table 1). In our institution, antithyroid medications are routinely withheld during the immediate period before and after 131I treatment. In 22 patients, however, the severity of the clinical symptoms warranted the institution of antithyroid medications 1–2 wk after 131I therapy. This group of patients included 21 cases of Grave’s disease and collectively accounted for only 5% of our patient population. Seventeen (77.3%) patients in this group responded favorably to 131I therapy, as compared to 83.6% for the entire population. The difference was not statistically significant. Thus, antithyroid medication in the post-therapy period was not considered to be a significant factor in our subsequent analyses.

Seventy-one patients (16.4%) remained hyperthyroid for a mean of 5.2 mo after an initial therapeutic dose of 131I; 57 had Graves’ disease and 14 had non-Graves’ disease (52 women, 19 men). Forty-two (59%) of the 71 patients who failed the initial 131I therapy had received antithyroid medications before 131I therapy (Table 1).

The parameters in the two groups are compared in Table 1. The magnitude of early 131I uptake and the early-to-late 131I uptake ratio was significantly greater in the patients who remained hyperthyroid. Male patients, those pretreated with antithyroid drugs, and those with non-Graves’ disease also showed significant correlation with an unsuccessful 131I therapy outcome. There were no statistically significant differences with respect to age, estimated weight of the gland, percent late...
TABLE 1

Comparison of Variables in Groups Successfully and Unsuccessfully Treated with Iodine-131

<table>
<thead>
<tr>
<th>Variable</th>
<th>Successful (n = 362)</th>
<th>Unsuccessful (n = 71)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (male) (%)</td>
<td>17</td>
<td>27</td>
<td>.059</td>
</tr>
<tr>
<td>Graves' disease (%)</td>
<td>89</td>
<td>80</td>
<td>.018</td>
</tr>
<tr>
<td>Pre-ATD Rx (%)</td>
<td>36</td>
<td>59</td>
<td>.018</td>
</tr>
<tr>
<td>Weight of gland (g)</td>
<td>59 ± 26</td>
<td>58 ± 22</td>
<td>.081</td>
</tr>
<tr>
<td>Total thyroxine (µg/dl)</td>
<td>16.7 ± 6</td>
<td>17.4 ± 8</td>
<td>.54</td>
</tr>
<tr>
<td>Free thyroxine (ng/ml)</td>
<td>3.6 ± 1.9</td>
<td>3.6 ± 2.3</td>
<td>.909</td>
</tr>
<tr>
<td>Early 131I uptake (%)</td>
<td>50 ± 24</td>
<td>66 ± 26</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>Late 131I uptake (%)</td>
<td>69 ± 16</td>
<td>71 ± 17</td>
<td>.28</td>
</tr>
<tr>
<td>4- to 24 hr 131I uptake ratio</td>
<td>0.70 ± 0.22</td>
<td>0.91 ± 0.31</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>Administered dose (µCi/g)</td>
<td>145 ± 93</td>
<td>155 ± 96</td>
<td>.51</td>
</tr>
</tbody>
</table>

*Statistical significance of the difference was tested with z-test (value >1.64 significant).

†Obtained from 362 patients whose thyroid weight was recorded.

‡Pre-ATD Rx = pretreatment with antithyroid drugs.

uptake of 131I, free and total thyroxine or therapeutic 131I dose per estimated gram of tissue.

Regression Analysis

The correlation between the outcome of 131I therapy and multiple independent variables, including age, sex, pretreatment with antithyroid drugs, clinical diagnosis and magnitude of the early and late 131I uptake were obtained using multiple linear regression analysis. The analysis aimed at estimating the relative contribution of each factor and identifying those that showed the strongest correlation. Both the early and late uptake values as well as the clinical diagnosis showed a statistically significant correlation with the outcome (Table 2).

A clinical diagnosis of Graves' disease was associated with a favorable outcome after 131I therapy, whereas a high 4-hr 131I uptake value or a low 24-hr 131I uptake value was a strong predictor of 131I therapy failure. The early-to-late 131I uptake ratio proved to be the strongest predictor of 131I therapeutic failure (coefficient = 0.43 and p < 0.01). Figure 1 shows the relationship between the 131I uptake ratio and the failure rate of 131I therapy for the entire patient population. The failure rate is fairly constant for uptake ratios of less than 1.0, but there is a dramatic increase in the failure rate when the uptake ratio is equal to 1.0 or greater. Figure 2 shows the relationship between the 4-hr percent uptake value and 131I therapy failure rate, and demonstrates that there was more variability in the 4-hr percent uptake value as a predictor of response to 131I therapy than in the 4- to 24-hr 131I uptake ratio.

A similar analysis was performed on the 362 patients whose estimated thyroid weights had been actually recorded in the chart at the time of therapy. The failure rate correlated significantly with the 131I uptake ratio as well as the clinical diagnosis, but not with the estimated weight of the thyroid gland. The regression model additionally included thyroxine and free thyroxine levels and administered dose per gram of thyroid, but the model did not show a significant association between these parameters and failure of 131I treatment.

DISCUSSION

The actual radiation dose delivered to thyroid tissue is the most important factor affecting outcome of 131I therapy in hyperthyroid patients (2,9-11). Other factors such as gender, race, age and size and nodularity of the thyroid gland also show a correlation with therapeutic outcome (2,9). In our study, two methods that might indicate the rate of thyroidal 131I turnover were evaluated as potential predictors of the outcome of 131I therapy. The early (4 to 6 hr) 131I uptake value and the 4- to 24-hr 131I uptake ratio were evaluated. The early-to-late 131I uptake ratio gave the best predictive index of 131I therapeutic outcome.

Almost 50% of the patients failed to respond to 131I therapy if the 131I uptake ratio was one or greater. The relationship, however, between 131I uptake ratios and therapeutic outcome was not linear. The likelihood of therapeutic failure for patients with a 4- to 24-hr 131I uptake ratio of less than 1.0 was relatively constant, ranging between 10% and 12%, whereas for patients with a 4- to 24-hr 131I uptake ratio equal to or greater than 1.0 the failure rate was 48% (Fig. 1).

There were three additional parameters identified that correlated with therapeutic outcome: prior treatment with antithyroid medications, gender and clinical type of hyperthyroidism. When a linear regression model was utilized to evaluate all parameters simultaneously, only the 4 to 24-hr 131I uptake ratio and the clinical type of hyperthyroidism were dominant discriminators. Patients with Graves' disease are more likely to have a successful response to therapeutic doses of 131I than those with non-Graves' disease (2,9,10).

The higher failure rate of 131I therapy among patients with an uptake ratio of >1.0 might be explained by the rapid clearance or turnover of 131I from the thyroid gland. This results in a shorter effective half-life of 131I with less radiation subsequently delivered to the gland. If patients with rapid thyroidal 131I turnover are treated with the usual dose of 131I, they are more likely to fail the initial treatment. It has been shown that use of 131I therapy doses of 3–10 mCi in patients with rapid 131I thyroidal turnover results in a 60% less radiation dose to the thyroid gland compared with those with relatively stable 131I uptake (2). A mean dose of about 28 mCi of 131I was required to deliver an adequate radiation dose for successful treatment in such patients.

Rapid 131I turnover has been ascribed to the so-called "small iodine pool syndrome," which can be seen in patients pretreated with antithyroid drugs, those who have undergone a subtotal thyroidectomy or unsuccessful 131I therapy, and those with T3 thyrototoxicosis (2,9,12,13). Becker and Hurley (2) reported that about 15% of their hyperthyroid patients had a very rapid 131I

TABLE 2

Multiple Linear Regression Analysis on Failure of Iodine-131 Treatment

<table>
<thead>
<tr>
<th>Variable</th>
<th>Six variant analysis without 4-24 hr 131I uptake ratio entered in the model*</th>
<th>Five variant analysis with 4-24 hr 131I uptake ratio replacing 4- and 24 hr % uptake values†</th>
<th>Coefficient</th>
<th>p-value</th>
<th>Coefficient</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>-0.00022</td>
<td>-0.000006</td>
<td>0.84</td>
<td></td>
<td>0.99</td>
<td></td>
</tr>
<tr>
<td>Pre-ATD Rx</td>
<td>0.08</td>
<td>0.063</td>
<td>0.09</td>
<td></td>
<td>0.076</td>
<td></td>
</tr>
<tr>
<td>Sex (male)</td>
<td>-0.008</td>
<td>-0.013</td>
<td>0.85</td>
<td></td>
<td>0.75</td>
<td></td>
</tr>
<tr>
<td>Diagnosis (GD)</td>
<td>-0.18</td>
<td>-0.19</td>
<td>&lt;0.01</td>
<td></td>
<td>&lt;0.01</td>
<td></td>
</tr>
<tr>
<td>4-hr % uptake</td>
<td>0.007</td>
<td>-0.19</td>
<td>&lt;0.01</td>
<td></td>
<td>&lt;0.01</td>
<td></td>
</tr>
<tr>
<td>24-hr % uptake</td>
<td>-0.006</td>
<td>-0.19</td>
<td>0.01</td>
<td></td>
<td>&lt;0.01</td>
<td></td>
</tr>
<tr>
<td>uptake</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4- to 24 hr 131I uptake ratio</td>
<td></td>
<td></td>
<td>0.43</td>
<td></td>
<td>&lt;0.01</td>
<td></td>
</tr>
</tbody>
</table>

*F = 9.8; significance of F < 0.00001.
†F = 11.5; significance of F < 0.00001.

Pre-ATD Rx = pretreatment with antithyroid drugs; GD = Graves' disease.
There have been conflicting published results about the effects of prior antithyroid drug therapy on the outcome of $^{131}$I therapy. Some studies have reported no effect (2,18-21), whereas others have reported a decreased incidence of hyperthyroidism after $^{131}$I treatment (5,11,22-25). In our study, 62% of patients with an $^{131}$I uptake ratio of $\geq 1.0$ had received antithyroid medications, whereas only 38% of patients with an $^{131}$I uptake ratio of less than 1 had received antithyroid medications ($p < 0.01$). This implies that antithyroid agents may alter $^{131}$I thyroidal kinetics by increasing $^{131}$I turnover.

Increased resistance to $^{131}$I therapy after the administration of antithyroid drugs has also been attributed to the radioprotective effect of the sulphydryl groups that are present in antithyroid medications (25-28). Recent studies indicate that pretreatment with carbimazole, which does not contain sulphydryl groups, is also associated with a higher incidence of recurrent or persistent hyperthyroidism (11,22). Carbimazole has been shown to reduce the effective half-life of thyroidal $^{131}$I (22,29). This change in intrathyroidal $^{131}$I kinetics may actually account for the increased failure rate of $^{131}$I therapy.

Thyroidal $^{131}$I uptake measurements in post-therapy patients have revealed considerable variability in $^{131}$I kinetics (30-32). In our patients, post-therapy $^{131}$I uptake measurements were obtained only in those who failed initial $^{131}$I therapy and had a second $^{131}$I treatment. Seventeen of 24 patients (71%) with an initial $^{131}$I uptake ratio of $\geq 1$ converted their $^{131}$I uptake ratio to <1 after the first therapeutic dose of $^{131}$I. Furthermore, 82% of these patients had a successful outcome after the second therapeutic dose of $^{131}$I.

There is currently no consensus among thyrologists as to the best therapeutic approach to be used in patients with rapid thyroidal $^{131}$I turnover to optimize the radiation dose delivered to the gland and to minimize the dose delivered to the bone marrow. It has not been clearly established if nonradioactive iodide, which induces a rapid decrease in circulating thyroxine and triiodothyronine (2,9,33), can be used routinely after $^{131}$I therapy to reduce the rate of thyroidal $^{131}$I turnover. Small doses of antithyroid medications taken after $^{131}$I treatment have also been shown to control clinical hyperthyroidism and reduce whole body radiation exposure (34). In addition, the use of lithium therapy, which blocks the secretion of thyroid hormone (35), needs to be investigated.

As with most retrospective studies, this study has certain shortcomings. The weight of the thyroid gland was estimated by palpation. Among experienced clinicians, the interobserver variability for estimates of thyroid gland size is 30% for small glands and greater for larger glands (4,36). The classification of the type of hyperthyroidism was based primarily on clinical judgment. Thus, it is possible that there was some overlap between the groups of patients with Graves' disease and those with non-Graves' disease.

**CONCLUSION**

The 4- to 24-hr $^{131}$I uptake ratio appears to be a practical index for predicting rapid $^{131}$I turnover in hyperthyroid patients. An $^{131}$I uptake ratio of $>1.0$, present in 15% of our patients, was associated with a near 50% initial $^{131}$I failure rate, whereas a ratio of $<1.0$ was associated with only an 11% failure rate. In patients with rapid $^{131}$I turnover, adjunctive measures such as iodide drops, low-dose antithyroid medications, or lithium after $^{131}$I therapy may be used to reduce the therapeutic dose of $^{131}$I. This would help minimize the whole-body radiation dose to the thyroid and maximize the therapeutic benefit.
We investigated and compared findings on combined ⁹⁹ᵐTc per-
technetate-²⁰¹Tl with those of ⁹⁹ᵐTc/pertechnetate-⁶⁷Ga scinti-
scans to elucidate the advantages of ²⁰¹Tl in detecting various
salivary glands disorders. Methods: We studied 23 patients: 6 had
sialadenitis, 12 had benign tumors and 5 had malignant tumors. All
but four patients had undergone ⁹⁹ᵐTc/pertechnetate (before and
after lemon stimulation). ²⁰¹Tl (early and delayed) and ⁶⁷Ga imaging.
Results: Five of six sialadenitis patients showed various degrees of
diffuse uptake of ⁹⁹ᵐTc. All six except one showed early uptake
without retention of ²⁰¹Tl on delayed imaging. The ⁶⁷Ga scan
showed uptake in all patients except one. Nine of 12 benign tumors
showed a cold defect on ⁶⁷Ga scans. Patients with Warthin's
tumors and plasmacytoma showed increased ⁹⁹ᵐTc uptake at the
tumor with Warthin's. The ²⁰¹Tl scan showed early uptake without
retention in benign tumors except in three patients, two of whom
had Warthin's tumor. Five of the benign tumors, however, were
positive on ⁶⁷Ga scan. None of the malignant tumors showed any
uptake of ⁹⁹ᵐTc. The ²⁰¹Tl scan showed uptake with tumor retention
on delayed images in three patients; three other patients also had positive
⁶⁷Ga scans. Overall, sensitivity and specificity of ²⁰¹Tl in
detecting malignant tumors were 60% and 73%, respectively, with
a negative predictive value of 85%. Sensitivity and specificity for ⁶⁷Ga
were 60% and 47%, respectively, with a negative predictive value of
80%. Conclusion: In view of sensitivity, specificity and convenience
of ²⁰¹Tl as well as future prospects for dual-isotope acquisition, ⁶⁷Ga
may be replaced by ²⁰¹Tl in detecting salivary gland disorder.

Key Words: salivary glands; technetium-99m; thallium-201; galli-
unium-67


The usefulness of ⁹⁹ᵐTc/pertechnetate to image the major salivary
glands is well-established and the introduction of ⁶⁷Ga-citrate imaging
has opened a new way of differentiating various pathological entities
involving the salivary glands (1–6). Gallium-67, however, has shown some limitations
in differentiating malignant from benign tumors (4.7). Thallium-
201-chloride has already shown its potential for detecting

Will Thallium-201 Replace Gallium-67 in Salivary Gland Scintigraphy?

Ali Syed Arbab, Kiyoshi Koizumi, Sachiko Hiraike, Keiji Toyama, Takao Arai and Tsutomu Araki
Department of Radiology, Yamanashi Medical University, Tamaho-cho, Nakakoma-gun, Yamanashi-ken, Japan

Received Oct. 13, 1995; revision accepted Feb. 28, 1996.
For correspondence or reprints contact: Ali Syed Arbab, Department of Radiology, Yamanashi Medical University, Tamahoko, Nakakoma-gun, Yamanashi-ken, 409-38, Japan.

COMBINED TECHNETIUM-99m/THALLIUM-201 AND TECHNETIUM-99m/GALLIUM-67 SCANS • Arbab et al. 1819