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High Dose ^{131}I Therapy for the Treatment of Hyperthyroidism Caused by Graves' Disease

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Radioactive iodine (^{131}I) has become the most widely used therapy for patients with hyperthyroidism caused by Graves' disease in the United States. There remains, however, significant variability among ^{131}I dosing regimens, and it is clear that most patients ultimately develop hypothyroidism after therapy. To avoid persistent hyperthyroidism, we adopted a high dose ^{131}I therapy protocol based on measurement of 24-h thyroid ^{123}I uptake designed to deliver 8 mCi (296 MBq) to the thyroid gland 24 h after ^{131}I administration. To evaluate the efficacy of this protocol, we reviewed our clinical experience over a 7-yr period.

We treated 261 patients (219 women and 42 men) with hyperthyroidism caused by Graves' disease with ^{131}I [mean dose, 14.6 mCi (540 MBq)] between 1993 and 1999. Before treatment, 207 (79%) had received an antithyroid drug (109 propylthiouracil and 98 methimazole). We determined their thyroid status 1 yr after treatment in relation to age, pretreatment with an antithyroid drug, pretreatment thyroid size, and dose of ^{131}I retained in the thyroid 24 h after treatment.

Among the 261 patients, 225 (86%) were euthyroid or hypothyroid 1 yr after treatment, and 36 patients (14%) had persistent hyperthyroidism and required a second treatment. The patients who had persistent hyperthyroidism were younger ($P < 0.01$), had larger thyroid glands ($P < 0.01$), higher pretreatment thyroid ^{123}I uptake values ($P < 0.01$), and higher serum T_4 concentrations ($P < 0.01$) and were more likely to have taken antithyroid medication before administration of ^{131}I ($P = 0.01$). Five of these patients developed transient hypothyroidism, followed by thyrotoxicosis. There was an asymptotic, inverse relationship between the retained dose of ^{131}I at 24 h and persistent hyperthyroidism, revealing a 5–10% failure rate despite delivery of up to 400 μCi (14.8 MBq)/g.

A dose of ^{131}I that results in accumulation of 8 mCi (296 MBq) in the thyroid gland 24 h after administration is an effective treatment for the majority of patients with Graves' hyperthyroidism. Young patients with larger thyroid glands, higher serum T_4 concentrations, and higher 24-h thyroid ^{123}I uptake values, and those pretreated with antithyroid medication for greater than 4 months are at higher risk for treatment failure. A higher dose of ^{131}I may be advisable in such patients. (*J Clin Endocrinol Metab* 87: 1073–1077, 2002)

RADIOACTIVE IODINE (^{131}I) has become the most widely used therapy for patients with hyperthyroidism due to Graves' disease in the United States (1). A number of dosing regimens have been proposed ranging from those based on high precision dosimetry and ultrasound-guided volume determination, to large, fixed doses of ^{131}I intended to cause hypothyroidism soon after treatment (2–7). Whatever the protocol, it is now clear that most patients ultimately develop hypothyroidism after ^{131}I treatment (8). Administration of relatively low doses of ^{131}I designed to restore euthyroidism, but not cause hypothyroidism may simply delay this or fail to cure the hyperthyroidism, thus necessitating additional treatment (9–11). Additionally, unless a program of annual contacts with the euthyroid group of patients is maintained, undiagnosed hypothyroidism may occur years later.

Since 1993, we have treated patients with Graves' hyperthyroidism with a dose of ^{131}I sufficient to cause hypothyroidism in 6–12 months in most patients, so as to minimize, if not eliminate, the likelihood of persistent hyperthyroidism. To achieve this we adopted a simplified dosing protocol based on 24-h thyroid ^{123}I uptake values with the goal of delivering 8 mCi (296 MBq) ^{131}I to the thyroid gland 24 h after ^{131}I administration. Given the difficulty of accurate assessment of thyroid size by physical examination, an estimate of size was not included in the dose calculation. To evaluate the utility of this protocol, we retrospectively reviewed the outcome 1 yr after administration of ^{131}I in 261 patients treated between 1993 and 1999.

Abbreviations: ATD, Antithyroid drug; FTI, free T_4 index; MMI, methimazole; PTU, propylthiouracil.

Subjects and Methods

Subjects

All patients who received initial ^{131}I therapy for Graves' disease in the Thyroid Treatment Center at the Brigham and Women's Hospital from 1993–1999 were evaluated. All patients had an elevated free T_4 index (FTI), suppressed TSH concentrations, and an elevated 24-h ^{123}I uptake. All patients were diagnosed with Graves' disease based on clinical findings, including the presence of hyperthyroidism and a diffuse goiter without nodules, with or without an isotopic scan. Data were collected from chart review, archived laboratory data, and, when needed, from discussion with the patients current primary physician or endocrinologist. Approval for laboratory and clinical review was obtained from the institutional review board of Brigham and Women's Hospital.

Clinical data before ^{131}I therapy

Baseline characteristics obtained include age at diagnosis, gender, and thyroid size relative to normal (20 g) as estimated by an endocrinologist (12, 13). Patients were categorized as having received propylthiouracil (PTU), methimazole (MMI), or no therapy before ^{131}I treatment. Duration of use as well as amount of time off therapy before ^{131}I administration was recorded. The serum T_4 concentration nearest to time of first diagnosis was recorded. The presence or absence of Graves' ophthalmopathy was assessed clinically.

Therapeutic regimen

Each patient received a 24-h radioiodine uptake with approximately 150 μCi ^{123}I 1 d before ^{131}I therapy. The dose of ^{131}I was calculated as follows: dose 131I = (8 mCi × 100)/(% uptake at 24 h). This dose was given to all patients regardless of prior antithyroid drug therapy (discontinued ~5 d before tracer administered), size of gland, or age of patient. All doses were determined and administered by two endocrinologists. We retrospectively calculated the dose retained at 24 h/g thyroid tissue using the estimated thyroid weight, the administered dose (micro-Curies) of ^{131}I, and the percent uptake at 24 h. In some patients, antithyroid medications (PTU, MMI) were restarted at least 7 d following ^{131}I therapy. Rarely (<10% of patients), saturated solution of potassium iodine (5 drops, twice daily) was given for rapid treatment or prevention of hyperthyroidism. When given, it was initiated at least 48 h after ^{131}I therapy. No patient had thyroid tenderness or the onset or worsening of Graves' ophthalmopathy in the first 6 months after therapy.

Follow-up after ^{131}I therapy

The primary outcome was each patient's thyroid status within 1 yr after ^{131}I therapy. Hypothyroid patients had a persistent, low FTI (T_4 × THBR) concentration (<5; normal, 5–11) and an elevated TSH (>15 μU/ml) within 12 months after therapy and had been started on levothyroxine replacement (to normalize TSH levels). Euthyroidism was defined as normal serum T_4 and TSH concentrations without levothyroxine therapy at 1 yr. A diagnosis of hyperthyroidism was made if the FTI remained elevated and TSH suppressed, or if the patient continued to require antithyroid medication.

Five patients experienced transient hypothyroidism followed by recurrent hyperthyroidism. These patients are included in the persistent hyperthyroidism group. Patients in this group included those with a low serum T_4 and elevated serum TSH concentrations at 2–6 months after ^{131}I therapy in the absence of antithyroid drug or inorganic iodide, who then experienced spontaneous recurrent thyrotoxicosis (T_4, >10 μg/dl; TSH, <0.03 μU/ml) within the following 1–4 months and required a second treatment.

Statistical analysis

Data are presented as the mean ± SD. Failure rates are presented as percentages of the total within each category examined. Unpaired *t* tests were used to compare continuous variables, and χ^2 tests were to compare discrete variables between groups. All statistical tests were two-sided. Significance was accepted at $P < 0.05$.

Results

Between 1993 and 1999 we treated 288 patients with Graves' hyperthyroidism. We were able to obtain follow-up data for 261 patients; their baseline characteristics are shown in Table 1. The average age was 42 yr, and the female to male ratio was 5.2:1. Thyroid size averaged approximately 50 g (2.5 times normal), and the average 24-h ^{123}I uptake was 58%. Before treatment, 109 patients (43%) received PTU, and 98 (39%) had received methimazole. Clinical Graves' ophthalmopathy was noted in 23% of patients; the vast majority were noted to be mild, consisting of exophthalmus and/or conjunctival irritation. All patients had stopped antithyroid drug (ATD) therapy before ^{131}I therapy, and most patients (83%) were off ATD for 5–7 d before ^{131}I treatment. All other patients were off ATD for greater than 7 d. The average dose of ^{131}I was 14.6 mCi (540 MBq), resulting in an estimated retained dose of 8.1 mCi (300 MBq) ^{131}I in the thyroid at 24 h. The average ^{131}I retained in the thyroid per estimated g of tissue at 24 h was 173 μCi/g [6.4 MBq; range, 50–450 μCi/g (1.8–16.6 MBq)].

At 1 yr, 225 patients (86%) were successfully treated (hypothyroid or euthyroid), and 36 (14%) remained hyperthyroid. Among the former group, 217 had persistent hypothyroidism (83%), and 8 (3%) were euthyroid. Among the hypothyroid group, 31 patients (12%) had persistent hyperthyroidism, and 5 (2%) had hypothyroidism, followed by recurrent hyperthyroidism. Of those successfully treated, over 90% responded to ^{131}I therapy within the first 6 months, as judged by biochemical analysis, symptom improvement, and/or decreasing requirements for antithyroid medications; the remainder responded within the first year.

There was a significant correlation between estimated thyroid weight and 24-h ^{123}I uptake ($P < 0.01$; data not shown). As expected because the estimated thyroid weight was not included in dose calculations, there was an inverse correlation between thyroid size and the dose of ^{131}I present at 24 h/g thyroid tissue ($P < 0.01$).

The success of treatment was directly related to the dose of ^{131}I retained per estimated g of thyroid tissue, but this relationship was not linear (Fig. 1). No patient became hypothyroid if the estimated 24-h dose was less than 80 μCi (3.0 MBq)/g The failure rate decreased progressively to reach approximately 10% at 128–155 μCi (4.7–5.7 MBq)/g. It did not decrease appreciably below that despite doses up to 400 μCi (14.8 MBq)/g thyroid at 24 h (Fig. 1).

TABLE 1. Baseline characteristics and outcome of ^{131}I treatment at 1 yr

	Total (n = 261)	Successful treatment (n = 225)	Treatment failure (n = 36)	*P* value
Gender (female/male)	5.2/1	5.2/1	5.0/1	0.92
Age at diagnosis (yr)	42 ± 16	43 ± 16	34 ± 14	<0.01
Thyroid size (g)	52 ± 22	48 ± 15	73 ± 41	<0.01
Serum T_4 (μg/dl)	16 ± 5	16 ± 5	19 ± 4	<0.01
24-h uptake (%)	58 ± 14	57 ± 14	66 ± 13	<0.01
Dose of ^{131}I (mCi)	14.6 ± 4.1	14.8 ± 4.2	13.1 ± 3.6	0.02
Dose ^{131}I to thyroid/g tissue (μCi/gm)	173 ± 60	178 ± 58	141 ± 59	<0.01
ATD before ^{131}I				
Yes (%)	82	79	100	0.01
No (%)	18	21	0	
Graves' ophthalmopathy				
Present (%)	23	17	58	<0.01
Absent (%)	78	83	42	

Comparisons of hypothyroid/euthyroid and hyperthyroid groups. All data expressed as the mean ± SD. Normal range for serum T_4, 5.0–10.5 μg/dl. To convert T_4 values to nmol/liter, multiply by 12.87. Normal range for thyroid ^{123}I uptake at 24 h, 5–35%.

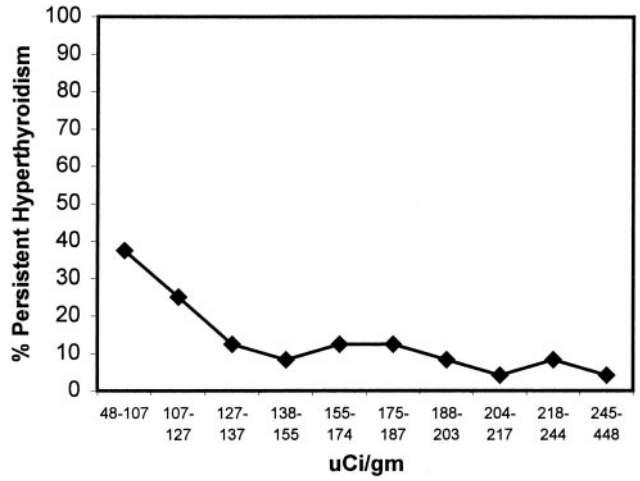

FIG. 1. Frequency of persistent hyperthyroidism as a function of estimated dose of ^{131}I in the thyroid gland 24 h after ^{131}I therapy in 261 patients (by decile).

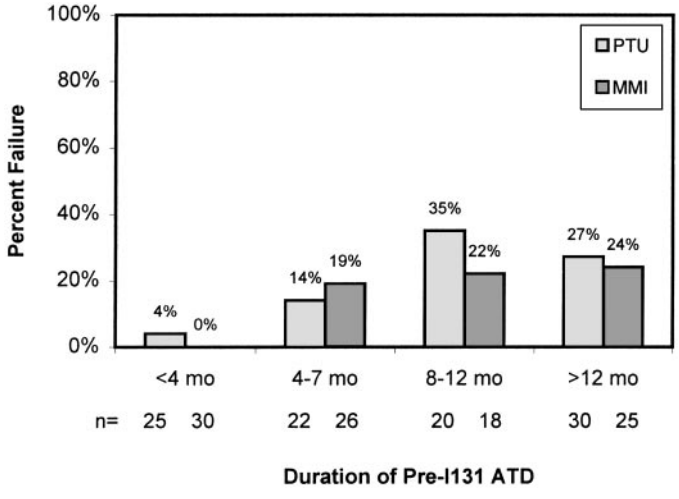

FIG. 2. Duration of ATD use before ^{131}I therapy and percentage of treatment failure.

Characteristics of patients with persistent hyperthyroidism

Compared with the patients treated successfully with a single dose, those who had persistent hyperthyroidism were younger and had larger thyroid glands, higher serum T_4 concentrations at diagnosis, higher 24-h ^{123}I thyroid uptakes, and a higher prevalence of ophthalmopathy (Table 1). The estimated retention of ^{131}I at 24 h was the same in both groups, but the dose of ^{131}I per estimated g of thyroid tissue was significantly lower in these patients than in those treated successfully.

All patients without exposure to ATD before ^{131}I therapy were successfully treated compared with only 79% of those who received ATD pretreatment ($P = 0.01$). Previous studies have indicated that PTU (but not MMI) pretreatment may reduce the efficacy of subsequent radioiodine therapy (14–17). Therefore, we separately analyzed the failure rate of patients pretreated with MMI and PTU for various time periods (Fig. 2). Only 1 of the 55 patients treated with an antithyroid drug (PTU) for less than 4 months failed treatment. In contrast, a significant fraction of patients pretreated with either PTU or MMI for 4 months or longer required a second treatment. There was no difference in patient characteristics or mean delivered dose of ^{131}I per g thyroid between PTU- and MMI-treated patients (PTU, 167 μCi/g; MMI, 176 μCi/g), suggesting that both drugs have the same effect.

Transient hypothyroidism with recurrent thyrotoxicosis

Five patients had transient hypothyroidism followed by recurrent hyperthyroidism. Compared with those with permanent hypothyroidism (Table 2), they were younger, had larger goiters, and had received PTU before radioiodine therapy. No patient became euthyroid and then had recurrent hyperthyroidism.

Discussion

Despite widespread use of ^{131}I therapy for patients with Graves' hyperthyroidism, there remains a lack of consensus regarding the optimal dose calculation. This is due to several factors, including differing goals of treatment (hypothyroidism *vs.* euthyroidism), and the lack of comprehensive studies relating the efficacy of different treatment protocols and outcomes (4). Given the need to prevent persistent hyperthyroidism and the high likelihood of eventual hypothyroidism after any protocol of ^{131}I therapy (18, 19), we concluded that the goal of therapy should be to induce hypothyroidism within 1 yr of therapy with a single dose of ^{131}I. Our treatment protocol was to deliver 150–175 μCi (5.5–6.5 MBq) ^{131}I/g thyroid tissue at 24 h. Assuming an average goiter weight of approximately 50 g, a dose of approximately 8 mCi (296 MBq) ^{131}I would need to be present in the thyroid at 24 h. This was achieved by adjusting the administered dose for the 24-h uptake. Our results support the efficacy of this regimen, in that 86% of the patients were euthyroid or hypothyroid at 1 yr after treatment.

TABLE 2. Baseline characteristics and initial ^{131}I treatment dose in patients who had transient hypothyroidism followed by recurrent hyperthyroidism, and patients who were permanently hypothyroid at 1 yr

	Transient hypo (n = 5)	Permanently hypo (n = 217)	*P* value
Gender (female/male)	5/0	5/1	0.32
Age at diagnosis (yr)	26 ± 14	42 ± 16	0.02
Thyroid size (g)	110 ± 82	48 ± 15	<0.01
Serum T_4 (μg/dl)	19.3 ± 3.2	16.3 ± 5.1	0.25
24-h uptake (%)	69 ± 13	57 ± 14	0.06
Dose ^{131}I (mCi)	12.4 ± 2.4	14.8 ± 4.2	0.24
Dose ^{131}I to thyroid/g tissue (μCi/g)	178 ± 57	0.02	
ATD therapy before ^{131}I			
PTU (%)	100	41	<0.01
MMI (%)	0	40	
None (%)	0	19	
Graves' ophthalmopathy			
Present (%)	40	22	0.35
Absent (%)	60	78	

Values are expressed as the mean ± SD. Normal range for serum thyroxine, 5.0–10.5 μg/dl. To convert T_4 values to nmol/liter, multiply by 12.87. Normal range for thyroid ^{123}I uptake at 24 h, 5–35%. *P* values are shown for comparisons between the two groups.

The results of other studies performed to evaluate the effectiveness of high dose, ablative radiotherapy for the treatment of Graves' disease have shown similar results (6, 7, 9, 20–23). Two of these are comparable in size to the present study. Kendall-Taylor *et al.* (7) examined 225 patients with Graves' hyperthyroidism treated with a standard dose of 15 mCi (555 MBq) ^{131}I and found 64% of the patients hypothyroid and 30% euthyroid 1 yr later. The subsequent appearance of hypothyroidism among the euthyroid group was not documented. Similarly, Nordyke *et al.* (9) examined the efficacy of various doses of ^{131}I in 605 patients and found 87% of those given 10 mCi (370 MBq) ^{131}I were euthyroid or hypothyroid 1 yr later. Successful therapy was inversely related to thyroid weight and directly related to the amount of ^{131}I per g thyroid tissue, although no other predictors of treatment success were found, including 24-h uptake. The effect of pretreatment with ATD was not included in the analysis.

We found that patients with persistent hyperthyroidism were younger; had a larger thyroid gland, a higher serum T_4 concentration, a higher 24-h uptake value, and more evidence of ophthalmopathy; and were more likely to have taken antithyroid medication before ^{131}I therapy compared with those who became hypothyroid or euthyroid. Although the dose of ^{131}I delivered per g thyroid was lower in the patients requiring a second dose of ^{131}I compared with those successfully treated with a single dose, it was equal to or higher than most current dosing recommendations in the literature (24, 25). Additionally, as demonstrated by the persistent failure rate (5–10%) despite estimated tissue doses at 24 h of up to 400 μCi (14.8MBq)/g, it is likely that the dose of ^{131}I alone does not explain the difference in outcome between the two groups.

Our data suggest a potential radioprotective effect of ATDs, as no patient who did not receive these failed initial treatment. Previous studies have raised this possibility for PTU. Imseis *et al.* (14) noted a cure rate of 24% 6–8 months after ^{131}I therapy in patients pretreated with PTU compared with approximately 60% if pretreatment was with MMI or patients had received no therapy. Similarly, Tuttle *et al.* (15) noted a 34% failure rate in patients pretreated with PTU compared with 4% of those receiving no ATD. Our study supports these findings, although our experience suggests that the radioprotective effects from short-term use of PTU ($<$4 months) are overcome by higher doses of ^{131}I.

Conversely, studies investigating the effects of pretreatment with MMI have suggested negligible radioprotective effects (14, 16, 17). Andrade *et al.* (17) showed no effect of MMI (median 12-wk treatment) on the outcome of radioiodine therapy compared with no MMI pretreatment. Similarly, Marcocci *et al.* (16) studied 274 patients treated with radioiodine and found no effect of pretreatment with MMI, although the duration of pretreatment was not specified. Our results are not consistent with these findings, as they suggest a radioprotective effect of MMI when given for 4 months or longer. We hypothesize that such an effect may not have been noted in prior studies because of a relatively short period of MMI pretreatment (16, 17). Nonetheless, the effects of MMI in our series are not qualitatively different from those of PTU, although the latter may have somewhat greater effect.

Five patients had transient hypothyroidism, followed by recurrent hyperthyroidism. Previous studies have reported similar findings in 1–6% of patients treated with radioactive iodine, although little has been mentioned regarding patient characteristics (26–28). Our study suggests that patients at risk for this pattern are similar to those who failed treatment without ever becoming hypothyroid. They are younger, have larger goiters, and have taken PTU before ^{131}I therapy. As expected from our dosing protocol, the average dose of ^{131}I delivered per g tissue at 24 h was significantly lower in this group. Although this value is comparable to doses recommended by some researchers (29), the low dose of ^{131}I per g tissue probably contributes to ineffective treatment. The probable pathophysiology of this event is transient radiation thyroiditis superimposed on a thyroid gland depleted of thyroid hormone by PTU therapy. Patients with elevated TSH should not be assumed to be permanently hypothyroid until at least 4 months have passed without recurrence, although they should receive replacement levothyroxine during this period.

In summary, high dose ^{131}I therapy based on 24-h radioiodine uptake is an effective treatment for patients with Graves' hyperthyroidism. This approach is safe, simple, and avoids the need for continuous long-term follow-up for later hypothyroidism in patients treated with lower doses. We believe, however, that a higher dose of ^{131}I is warranted in select patients and now aim to deliver 11 mCi (402 MBq) ^{131}I to the thyroid at 24 h in patients with features suggesting more severe hyperthyroidism, as indicated by gland size more than 4 times normal, age less than 20 yr, or 24-h uptake values of 70% or higher, especially if these patients have received pretreatment with ATD for more than 4 months. Despite these modifications, a failure rate between 5–10% seems unavoidable with a single treatment, and patients and their physicians should be informed accordingly.

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