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The Effect of Antithyroid Drug Pretreatment on Acute Changes in Thyroid Hormone Levels after ^{131}I Ablation for Graves' Disease*

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ABSTRACT

Acute changes in thyroid hormone levels before and after radioiodine therapy for Graves' disease were compared in 42 patients randomized to receive either antithyroid drug pretreatment or no pretreatment. Five patients (11.9%), including 3 in the pretreatment arm and 2 in the no pretreatment arm experienced a late exacerbation of thyrotoxicosis after radioiodine therapy. The majority (19 of 21, 90.5%) of pretreated patients experienced a transient increase in free T_4 and free T_3 after discontinuation of antithyroid drugs, with little further elevation after radioiodine therapy. After stopping antithyroid drugs and before radioiodine administration, mean serum free T_4 values rose from 14.7 ± 6.9 to 21.6 ± 12.1 pmol/L, representing a 46.9% increase, whereas serum free T_3 levels rose from 4.9 ± 1.7 to 8.1 ± 6.3 pmol/L, representing a 65.3% increase. The average pretreated patient experienced a 52.4% increase [95% confidence interval (CI), +26.4% to +78.5%] in free T_4 and a 61.8% increase (95% CI, +23.5% to +100.0%) in free T_3. Conversely, the majority (19 of 21, 90.5%) of nonpretreated patients experienced a rapid decline in thyroid hormone levels after radioiodine treatment. Over the 14 days after radioiodine therapy mean free T_4 values in nonpretreated patients fell from 85.8 ± 60.4 to 58.0 ± 76.5 pmol/L, representing a 32.4% decrease, whereas mean free T_3 levels fell from 16.1 ± 8.0 to 10.8 ± 11.1 pmol/L, representing a 32.9% decrease. The average nonpretreated patient experienced a 20.6% decrease (95% CI, −47.3% to +7.0%) in free T_4 and a 24.3% decrease (95% CI, −1.2% to −47.4%) in free T_3 during this time period. Excluding 2 patients with a late exacerbation after radioiodine, 19 nonpretreated patients experienced a decrease in mean free T_4 values from 76.8 ± 46.6 to 36.6 ± 19.8 pmol/L, representing a 52.3% decrease, whereas mean free T_3 levels fell from 15.5 ± 7.7 to 7.8 ± 3.6 pmol/L, representing a 49.7% decrease. The average decrease in free T_4 levels among this subgroup of patients was 30.1% (95% CI, −4.6% to −55.6%), whereas the average decrease in free T_3 was 34.4% (95% CI, −13.7% to −55.1%). High levels of TSH receptor autoantibodies at diagnosis were associated with an acute worsening of thyrotoxicosis after stopping antithyroid drug pretreatment. We conclude that pretreatment with antithyroid drugs does not protect against worsening thyrotoxicosis after radioiodine, but may allow such patients to start from a lower baseline level should an aggravation in thyrotoxicosis occur. The findings support the recommendation that most patients with Graves' disease do not require antithyroid drug pretreatment before receiving radioiodine. (*J Clin Endocrinol Metab* **86:** 3016–3021, 2001)

RADIOIODINE THERAPY is the most common treatment for Graves' disease employed in the United States (1). After delivery of a single intrathyroidal radiation dose approximating 15,000 rads, 80–90% of treated patients will become hypothyroid over the ensuing 2–4 months. The effectiveness of radioiodine therapy stems from its ability to cause an intense radiation thyroiditis and subsequent fibrosis, thereby destroying the synthetic capacity of the thyroid (2). A release of stored thyroid hormone into the circulation may occur after radioiodine therapy, presumably as a result of follicular cell disruption. Worsening thyrotoxicosis and even thyroid storm have been reported after radioiodine therapy (3). As a result, many patients are given antithyroid drugs before radioiodine therapy in an attempt to prevent a transient worsening of their thyrotoxicosis. A survey of members of the American Thyroid Association found that 31% of respondents would prescribe antithyroid drugs before treatment with radioiodine (4). However, antithyroid drug therapy is associated with several potential side-effects, including rash, hepatic injury, and agranulocytosis (5). Further, pretreatment with antithyroid drugs increases the risk of radioiodine failure (6–8).

In a previous prospective nonrandomized study we found that the acute changes in thyroid hormones observed in pretreated patients receiving radioiodine occurred as a result of stopping antithyroid drugs in preparation for ablation therapy, rather than as a result of the radioiodine therapy itself (9). Specifically, an approximate doubling of free thyroid hormone levels was found to occur over the 6 days after stopping antithyroid drugs, with little further increase after radioiodine therapy. Conversely, a smaller group of nonpretreated patients experienced rapid decreases in free thyroid hormone levels after radioiodine. The aim of the present study was to examine this issue in a prospective randomized trial.

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Subjects and Methods

Patients

Patients with a new diagnosis of Graves' disease, defined as diffuse goiter, thyrotoxicosis, and, in most cases, elevated radioactive iodine uptake (RAIU) and positive TSH receptor autoantibodies, were approached for study entry. Patients were excluded for age less than 18 yr or greater than 65 yr, prior treatment for thyrotoxicosis, moderate to severe ophthalmopathy, and known cardiovascular disease or other significant comorbid illness. The study was approved by the investigational review boards and human use committees at the two participating centers.

Laboratory study

Free T_4 was measured using direct equilibrium dialysis kits obtained from Nichols Institute Diagnostics (San Juan Capistrano, CA). Free T_3 levels were measured using the Coat-A-Count direct single tube solid phase RIA supplied by Diagnostic Products (Los Angeles, CA). Serum TSH was measured using the LumaTag Chemiluminescence Immunometric Assay from London Diagnostics (Eden Prarie, MN). Luminometric readings were obtained on the AutoClinLumat LB-952 (Berthold, Inc., Nashua, NH). Serum thyroid-stimulating Ig (TSI) and TSH binding inhibitory Ig titers, were obtained in 25 and 19 patients, respectively, at the time of diagnosis or study entry and were run at Nichols Institute Diagnostics using CHO cells transfected with the complementary DNA from the TSH receptor and a RRA, respectively. RAIU, determined in 37 patients, was measured at 24 h after ingestion of 7.5–10.0 μCi ^{131}I. The normal ranges were as follows: free T_4, 10.3–30.6 pmol/L; free T_3, 1.5–6.9 pmol/L; TSH, 0.51–5.0 mIU/L; TSI, less than 130%; TSH binding inhibitory Ig, less than 10%; and RAIU, 8–30%.

Treatment protocol

Randomization and β-adrenergic blockade. Randomization was performed using a computerized random number generator. All patients were placed and maintained on β-adrenergic blockers (generally atenolol, 50–100 mg daily) throughout the study period.

Antithyroid drug therapy. Pretreated patients were given methimazole in a dose of 30 mg once daily, which was then adjusted based on serial thyroid function tests performed at 2-week intervals. All pretreated patients received antithyroid drugs for a minimum of 2 months and until free T_4 levels were within the normal range.

Radioiodine therapy. Pretreated patients had not taken antithyroid drugs for 6 days at the time of radioiodine ablation. Nonpretreated patients generally received radioiodine ablation within 1 week of initial evaluation. The amount of radioiodine administered for treatment was determined in a nonblinded fashion (due to local policy) using a baseline dose of 15 mCi, with 5–15 mCi added for patients with estimated goiter size greater than 60–80 g or a RAIU less than 30%, and 3–5 mCi subtracted for patients with estimated goiter size of less than 30 g.

Testing protocol

Baseline free T_4 and free T_3 were measured in pretreated patients 6 days before radioiodine therapy, which was approximately 24 h after stopping antithyroid drugs. Both pretreated and nonpretreated patients were tested on the day of radioiodine ablation and on days 1, 3, 5, 7, and 14 after receiving radioiodine.

Statistical analysis

Baseline laboratory and clinical features were compared using a χ^2 test for categorical variables and the Mann-Whitney test for continuous variables. Free T_4 and free T_3 values over the study period were analyzed using ANOVA with repeated measures. To satisfy assumptions of normality, the logarithmically transformed free thyroid hormone values were used. As the sphericity of the data could not be assumed, the corrected (Greenhouse-Geisser) probabilities were used. Spearman rank coefficient was used to explore associations between the maximum change in thyroid hormone levels and patient demographics.

Results

Patient characteristics

Forty-four (34 women and 10 men) patients were recruited and randomized for the study. These patients were either seen initially in the authors' practices or referred for study entry from other health care providers at both centers. Among these, 1 patient withdrew after deciding against radioiodine ablation, and 1 patient was excluded due to failure to report for phlebotomy on several testing dates. No systematic record was kept of patients who declined referral for study involvement. A total of 42 patients (33 women and 9 men) completed the study, including 31 patients at study site 1 (Walter Reed Army Medical Center) and 11 patients at study site 2 (Sinai Hospital). Patient characteristics in pretreated and nonpretreated groups are shown in Table 1. These groups were similar in terms of age, gender distribution, goiter size, RAIU, and TSH receptor antibody titers; however, nonpretreated patients had slightly higher free T_4 levels than pretreated patients at the time of initial diagnosis.

Changes in mean thyroid hormone levels

Changes in free T_4. Figure 1 shows changes in mean free T_4 values in the pretreated and nonpretreated patient groups. In pretreated patients, after stopping antithyroid drugs but before radioiodine administration, mean free T_4 levels rose significantly from 14.7 ± 6.9 to 21.6 ± 12.1 pmol/L, representing a 46.9% increase in mean values ($P < 0.0005$). The average pretreated patient experienced a 52.4% increase (95% CI, +26.4% to +78.5%) in free T_4 during this time period, with peak free T_4 obtained on day 3 after radioiodine. The upper limit of normal for free T_4 was exceeded in 23.8% of patients before receiving radioiodine and in 33.3% of patients 1 day after radioiodine. The additional increase in thyroid hormone levels occurring after radioiodine did not achieve significance. After attaining peak values, there was a rapid and significant decrease in mean free T_4 levels into the mid-normal ranges.

The majority (19 of 21, 90.5%) of nonpretreated patients experienced a rapid decline in thyroid hormone levels after radioiodine. Over the 14 days after radioiodine therapy mean free T_4 values in nonpretreated patients fell from 85.8 ± 60.4 to 58.0 ± 76.5 pmol/L, representing a 32.4% decrease ($P <$

TABLE 1. Features of the patients

Feature	Pretreatment	No pretreatment	*P* value
No. of patients	21	21	
Gender (F:M)	14:7	19:2	NS
Age (yr)	42 ± 13	36 ± 9	NS
Baseline free T_4 (pmol/L)	52 ± 40	80 ± 45	0.04
RAIU (% at 24 h)	50 ± 16	60 ± 18	NS
Goiter (S:M:L)	5:9:7	4:9:8	NS
TSI (%)	162 ± 91	201 ± 104	NS
TBII (%)	33.1 ± 22.9	42.6 ± 36.4	NS
Dose of ^{131}I (mCi)	16.3 ± 3	16.6 ± 4	NS

S, Small goiter (<30 g); M, medium goiter (31–60 g); L, large goiter (>60 g); RAIU, radioactive iodine uptake at 24 h; TSI, thyroid-stimulating Ig; TBII, TSH binding inhibitory Ig. Normal ranges for laboratory values are as follows: free T_4, 10.3–30.6 pmol/L; RAIU, 8–30%; TSI, <130%; and TBII, <10%.

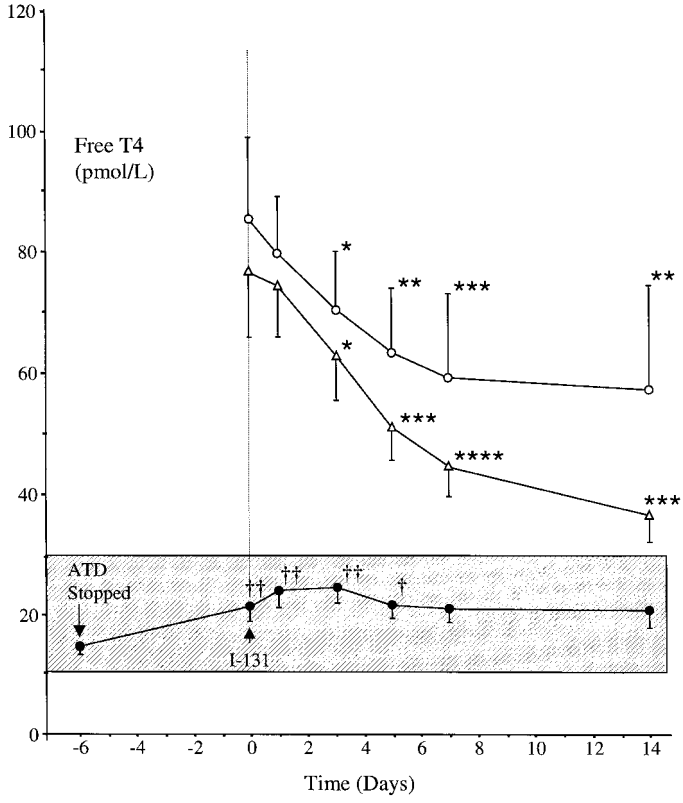

FIG. 1. Changes in serum free T_4 levels in 21 antithyroid drug-pretreated patients (●), 21 nonpretreated patients (○), and the subgroup of 19 nonpretreated patients not experiencing worsening thyrotoxicosis after radioiodine (△). Values shown represent the mean; *bars* indicate the SEM. The normal range for free T_4 is shown by *cross-hatching*. *, $P < 0.05$; **, $P < 0.$; ***, $P < 0.005$; ****, $P < 0.0005$ [compared with T-0 (the day of radioiodine treatment)]. †, $P < 0.005$; ††, $P < 0.0005$ [compared with T-6 (the day of antithyroid drug discontinuation)].

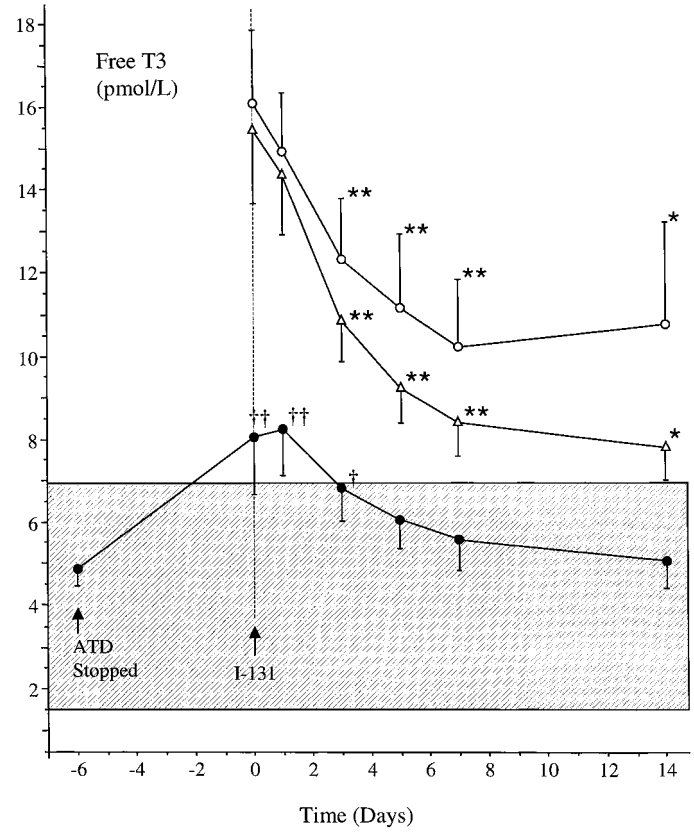

FIG. 2. Changes in serum free T_3 levels in 21 antithyroid drug-pretreated patients (●), 21 nonpretreated patients (○), and a subgroup of 19 nonpretreated patients not experiencing worsening thyrotoxicosis after radioiodine (△). Values shown represent the mean; *bars* indicate the SEM. The normal range for free T_3 is shown by *cross-hatching*. *, $P < 0.005$; **, $P < 0.0005$ [compared with T-0 (the day of radioiodine treatment)]. †, $P < 0.01$; ††, $P < 0.005$ [compared with T-6 (the day of antithyroid drug discontinuation)].

0.01). The average nonpretreated patient experienced a 20.6% (95% CI, −47.3% to +7.0%) decrease in free T_4 during this period. Excluding 2 patients with a late exacerbation after radioiodine, 19 nonpretreated patients experienced a decrease in free T_4 values from 76.8 ± 46.6 to 36.6 ± 19.8 pmol/L, representing a 52.3% decrease ($P < 0.005$). The average decrease for free T_4 among this subgroup of patients was 30.1% (95% CI, −4.6% to −55.6%).

Changes in free T_3. Free T_3 levels rose more rapidly and to a greater extent and showed an earlier peak than free T_4 levels after cessation of antithyroid drugs. Figure 2 shows changes in mean free T_3 values in pretreated and nonpretreated patients. In pretreated patients, after stopping antithyroid drugs and before radioiodine administration, mean free T_3 levels rose significantly from 4.9 ± 1.7 to 8.1 ± 6.3 pmol/L, representing a 65.3% increase in mean values ($P < 0.005$). The average pretreated patient experienced a 61.8% increase (95% CI, +23.5% to +100.0%) in free T_3 during this time period, peaking 1 day after radioiodine. The upper limit of normal for free T_3 was exceeded in 38.1% of patients before receiving radioiodine and in 42.9% of patients 1 day after radioiodine.

In nonpretreated patients, over the 14 days following radioiodine therapy, mean free T_3 levels fell from 16.1 ± 8.0 to 10.8 ± 11.1 pmol/L, representing a 32.9% decrease ($P < 0.005$). The average patient experienced a 20.7% decrease (95% CI, −13.7% to −55.1%) in serum free T_3 during this time period. Excluding 2 patients with a late exacerbation after radioiodine, 19 nonpretreated patients experienced a decrease in free T_3 levels from 15.5 ± 7.7 to 7.8 ± 3.6 pmol/L, reflecting a 49.7% decrease ($P < 0.005$). The average patient in this subgroup experienced a 34.4% decrease (95% CI, −13.7% to −55.1%) in serum free T_3 levels during this time period.

Comparison of the rates of change in pretreated and nonpretreated patients. As expected, mean free T_4 and free T_3 levels were higher in the nonpretreated patients at each time point in the study. The rate of improvement in free T_4 levels over the 2 weeks following radioiodine ablation was greater in nonpretreated patients than in pretreated patients ($P = 0.041$), but the rates of change in free T_3 were similar in the two groups ($P = 0.36$).

Individual patient data. Analysis of individual patient data showed that a small subset of patients (three pretreated and two nonpretreated patients) experienced a continuous rise in

thyroid hormone levels throughout the study period after receiving radioiodine therapy (Fig. 3). One nonpretreated patient in this category had refractory hyperthyroidism and ultimately required three doses of radioiodine for control. One pretreated patient with worsening thyrotoxicosis after radioiodine was placed back on antithyroid drugs and ultimately required a second dose of radioiodine before becoming hypothyroid. The three remaining patients with worsening thyrotoxicosis after radioiodine treatment, including one nonpretreated and two pretreated patients, became hypothyroid within 2 months of receiving radioiodine.

Clinical parameters associated with changes in thyroid hormone

Patient clinical and laboratory features were examined for associations with the acute rise in thyroid hormone levels in the pretreatment group and in patients experiencing late worsening of thyrotoxicosis after radioiodine. Table 2 summarizes the associations examined and findings in pretreated patients. In these patients, TSI titers were positively correlated with increases in free T_4 ($P = 0.024$) and free T_3 ($P = 0.001$) after stopping antithyroid drugs. No correlation was found for patient age, gender, goiter size, RAIU, or thyroid hormone levels at diagnosis. Figure 4 shows the relationship between TSI titers and change in free T_3 values in pretreated patients. It is of note that TSI titers were lower than the reported upper limit of normal of 130% in eight of these patients, which is in keeping with our previous observations on the current sensitivity of this assay (10). In five patients experiencing worsening thyrotoxicosis after radioiodine therapy, only male gender was significantly associated, with three of five (60%) patients being males compared with an overall male representation in the study of only 21% ($P = 0.03$).

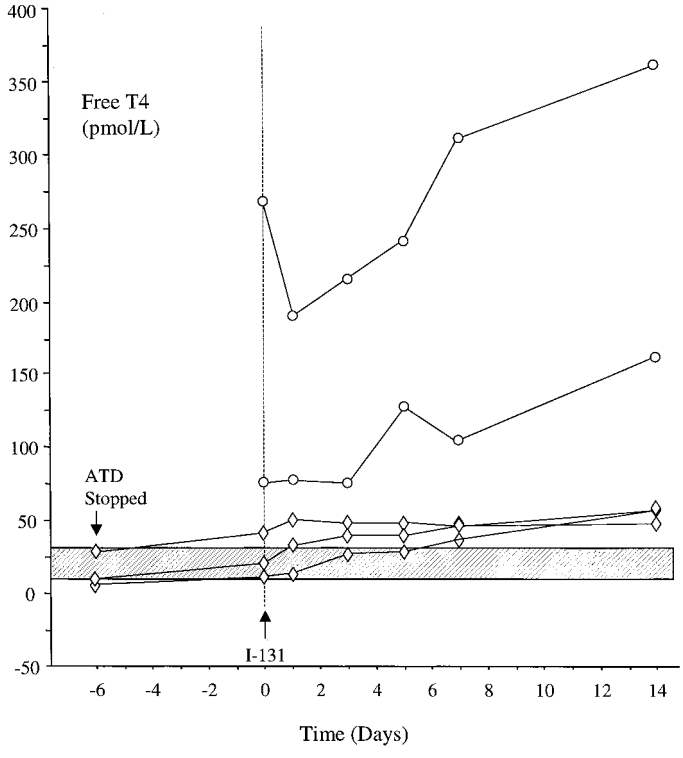

FIG. 3. Changes in free T_4 levels in five patients experiencing worsening thyrotoxicosis after radioiodine therapy, including three pretreated patients (◇) and two nonpretreated patients (○). The normal range for free T_4 is shown by *cross-hatching*.

TABLE 2. Association between clinical parameters and serum free T_4 and free T_3 responses to antithyroid drug discontinuation in pretreated patients

Clinical feature	Change in free T_4		Change in free T_3	
	r	*P*	r	*P*
Age	0.114	NS	−0.017	NS
Gender	NA	NS	NS	NS
Goiter size	0.238	NS	0.359	NS
Free T_4 at diagnosis	0.267	NS	0.089	NS
Free T_3 at diagnosis	0.557	NS	0.530	NS
TSI	0.577	0.024	0.758	0.001
Anti-TPO	−0.338	NS	−0.012	NS
RAIU	0.356	NS	0.404	0.052
Duration of pretreatment	0.148	NS	−0.02	NS
Radioiodine dose	0.186	NS	0.186	NS

NA, Not applicable to discontinuous variable; TSI, thyroid-stimulating Ig; anti-TPO, antithyroid peroxidase; RAIU, radioiodine uptake; NS, not significant at $P < 0.05$.

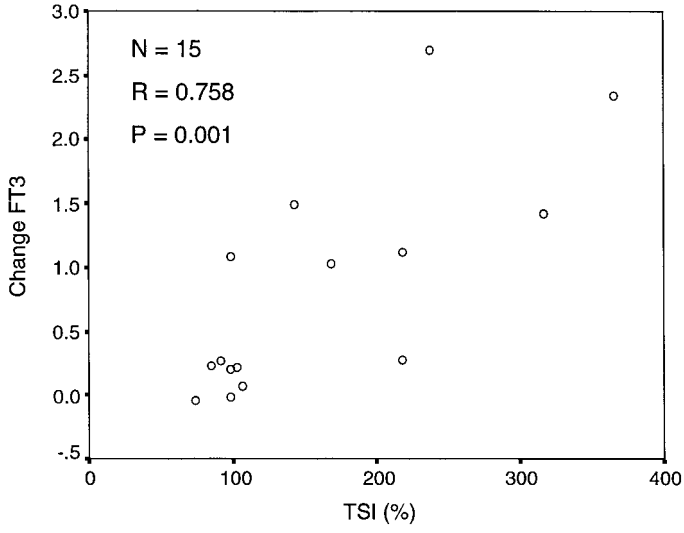

FIG. 4. Relationship between serum TSH receptor autoantibody (TSI) and acute increase in serum free T_3 after stopping antithyroid drugs in Graves' disease patients receiving pretreatment. FT_3, Free T_3.

Discussion

The rationale generally given for pretreatment with antithyroid drugs before radioiodine is to deplete thyroid hormone stores and theoretically reduce the risk of worsening thyrotoxicosis or even thyroid storm after radioiodine therapy (11). However, the risk of aggravating thyrotoxicosis after radioiodine for thyrotoxicosis is probably small, and it is not clear whether this risk is diminished by pretreatment with antithyroid drugs. McDermott and colleagues reviewed the medical literature with reference to cases of thyroid storm after radioiodine therapy for thyrotoxicosis (3). These researchers found that 0.34% of 2975 patients treated with

radioiodine for thyrotoxicosis experienced thyroid storm, and 0.88% experienced moderate or severe exacerbation of thyrotoxicosis (3). Approximately half of the cases reviewed by these researchers were pretreated with antithyroid drugs before receiving radioiodine, although not all of these patients were known to be euthyroid before antithyroid drug discontinuation.

Data available from nonrandomized trials in this area are somewhat conflicting. Maloof and Chapman did not find aggravation of disease after radioiodine therapy in 47 patients with cardiac manifestations of thyrotoxicosis, only 2 of whom had received antithyroid drug pretreatment (12). Wise and colleagues found an early fall in thyroid hormone levels in each of 50 patients with Graves' disease treated with 10–15 mCi radioiodine without antithyroid drug pretreatment (13). Creutzig and colleagues followed 46 hyperthyroid patients with diffuse goiter receiving radioiodine without antithyroid drug pretreatment and noted only slight increases in serum T_3 levels for the group as a whole, occurring 1 day after radioiodine therapy (14). Interestingly, progressive worsening of thyrotoxicosis occurred in 3 of 46 (7%) patients after radioiodine therapy, and was not related to goiter size or the dose of radioiodine delivered (14). More recently, Graves' disease patients assessed with thyroid function testing every 2 weeks after ablation therapy were noted to sustain transient increases in free T_4 levels at 4–6 weeks in 36% of nonpretreated patients and earlier increases at 2 weeks in 53% of pretreated patients (15). Another nonrandomized study noted asymptomatic increases in thyroid hormone levels in 29% of 21 patients with Graves' disease receiving radioiodine without antithyroid drug pretreatment, although the magnitude of this change was not given, and mean thyroid hormone levels actually decreased immediately after radioiodine (16). In summary, the published literature suggests that worsening thyrotoxicosis after radioiodine is rare, and when it does occur, it is generally subclinical.

Another rationale for the use of antithyroid drug pretreatment before radioiodine for Graves' disease is the belief that a more rapid control of thyrotoxicosis may be obtained after radioiodine therapy (17, 18). However, this fails to take into account the weeks or months of pretreatment during which time the patient has persistent thyrotoxicosis. Further, data previously published by us (9) and others (17) shows a rapid decrease in thyroid hormone levels after radioiodine therapy in nonpretreated patients. This rapid response may in part reflect the use of larger, ablative doses of radioiodine rather than smaller doses in an attempt to restore euthyroidism. Therefore, this second rationale for pretreatment with antithyroid drugs is not supported by published data.

In addition to a lack of proven benefit, pretreatment with antithyroid drugs before radioiodine may lead to unwanted effects, such as an increased risk of radioiodine failure (6–8) and worsening thyrotoxicosis after abrupt discontinuation of these medications in preparation for radioiodine (19). A recent study has suggested that radioiodine failure after antithyroid drug pretreatment may be more problematic with the use of propylthiouracil than with methimazole (20). As antithyroid drugs irreversibly inhibit thyroid peroxidase (21), they are generally stopped several days before radioiodine administration to allow incorporation of this isotope into thyroid hormone (5). Attempts to administer radioiodine therapy without stopping antithyroid drugs have resulted in treatment failure rates approaching 90% (22).

Our earlier prospective nonrandomized study (9) disclosed remarkably similar results to those of the present prospective randomized trial, although the former study was designed primarily to investigate acute changes occurring in pretreated patients. A study similar to ours was recently reported by Andrade and colleagues, in which patients received either methimazole or no pretreatment before radioiodine therapy (17). As in our study, Andrade and colleagues noted a small group of patients with worsening thyrotoxicosis after radioiodine therapy in 13.0% and 7.1% of the pretreated and nonpretreated groups, respectively. Unlike our current study, Andrade and colleagues failed to detect any association between clinical or laboratory parameters and changes in thyroid hormone levels after stopping antithyroid drugs (17).

When is pretreatment helpful or warranted? As worsening thyrotoxicosis after radioiodine therapy occurred in approximately 10% of patients with or without pretreatment, it is apparent that pretreatment did not prevent this exacerbation. However, pretreatment did allow such patients to start from a lower baseline value, making it less likely that a theoretical decompensation threshold would be reached. Conversely, it could be argued that the most rapid increase in thyroid hormone levels occurred after stopping antithyroid drug pretreatment. Further, many known precipitants of thyroid storm, such as discontinuation of antithyroid drugs, thyroidectomy, radioiodine therapy, and vigorous palpation of the thyroid, lead to systemic decompensation through this mechanism (19). It is not known which of these two situations presents the greatest threat to the patient. Another consideration involves a comparison of the total duration of thyrotoxicosis in pretreated and nonpretreated patients. Although this was not a specific end point in our study, our data show that mean free T_4 and mean free T_3 levels in nonpretreated patients rapidly approached the normal range over the 14-day period that followed radioiodine administration. Conversely, pretreated patients generally required 4–8 weeks or more to establish euthyroidism before becoming eligible for radioiodine. The delay in correction of thyrotoxicosis imposed by pretreatment rather than direct radioiodine ablation represents a window during which pretreated patients are at risk for ill effects from thyrotoxicosis, including atrial fibrillation and associated embolic phenomenon.

Our study did not include a comparison of symptom scores in the two treatment arms; however, both the previous study by our group (9) and the study by Andrade and colleagues (17) failed to find significant correlations between symptoms and thyroid hormone changes after stopping antithyroid drugs in pretreated patients. It is likely that the β-adrenergic blockade therapy used in both studies significantly attenuated the change in symptoms that might have otherwise occurred (23). The radioiodine dosage in our study was selected empirically rather than on the basis of dosimetry (24) or exact measurement of thyroid volume. Our rationale for this was 2-fold. First, it was our intention to simulate current clinical practice. Eighty-five percent of respondents to a survey of American Thyroid Association

members used a semiquantitative approach similar to ours for radioiodine dose selection in patients with Graves' disease (4). Second, it has been repeatedly demonstrated that complex dosimetric techniques fail to reliably determine a set delivered tissue dose of radioactivity to the thyroid (24–26), due to as much as 45% patient-to-patient variability in radioiodine organification, which cannot be predicted on the basis of either gland size or RAIU (25). A recent comparison of a fixed dose of radioiodine (15 mCi) to a calculated dose designed to deliver 100 Gy to the thyroid found a success rate of 71% using a fixed dose compared with only 58% using a calculated dose (26). Although thyroid size was estimated on the basis of examination by an experienced thyroidologist at both study sites, intersite reproducibility was not specifically assessed.

In summary, pretreatment with antithyroid drugs before radioiodine ablation therapy results in a rapid increase in thyroid hormone levels upon stopping these medications in preparation for radioiodine. Direct use of radioiodine without pretreatment results in a rapid reduction in thyroid hormone levels, often approaching the normal range within 2 weeks of therapy. Pretreatment with antithyroid drugs does not protect against worsening thyrotoxicosis after radioiodine therapy, but allows such patients to start from a lower baseline value. It is our opinion, therefore, that most patients with Graves' disease should not be pretreated with antithyroid drugs before receiving radioiodine. Whether patients with underlying coronary artery disease or other comorbid conditions benefit from pretreatment is not known, because, on the one hand, pretreatment exposes these patients to the risk of prolonged hyperthyroidism as well as an acute rise in free hormone levels after stopping antithyroid drugs, whereas, on the other hand, pretreatment provides a measure of protection by establishing lower baseline values should an exacerbation occur.

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