

Effect of Methimazole Pretreatment on Serum Thyroid Hormone Levels after Radioactive Treatment in Graves' Hyperthyroidism*

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ABSTRACT

Radioiodine (^{131}I) is the preferred definitive treatment for Graves' hyperthyroidism. Pretreatment with antithyroid drugs is often used to avoid thyroid hormone discharge after ^{131}I ablation. However, this may represent an unnecessary increase in risk and costs. Fifty-one patients with Graves' disease were randomly assigned to receive ^{131}I alone (28 patients) or ^{131}I plus pretreatment with methimazole (30 mg/day; 23 patients). Methimazole was interrupted 4 days before ^{131}I therapy. Serum T_4 , free T_4 (FT_4), and T_3 were measured on days -4 and -1, on the day of treatment, and on days 2, 5, 7, 14, 20, and 30.

In patients receiving ^{131}I alone, mean serum T_4 levels did not change after therapy. Mean serum FT_4 and T_3 levels decreased significantly 5 days after ^{131}I administration (15% and 18%, respective-

ly). Serum T_3 reached its lowest level on day 30 (38%). With pretreatment, mean serum T_4 , FT_4 , and T_3 levels increased (38%, 39%, and 70%, respectively) after methimazole discontinuation and before ^{131}I administration. After ^{131}I , serum T_4 levels peaked on day 7 (23% vs. treatment day; 70% vs. baseline); FT_4 levels peaked on day 14 (53% vs. treatment day; 107% vs. baseline). The serum T_3 concentration increased 9% on day 2 (85% vs. baseline) and decreased from day 14 (15%) to day 30 (21%). We conclude that interruption of antithyroid drugs causes a short term increase in serum thyroid hormone levels in patients with Graves' hyperthyroidism receiving ^{131}I . Thyroid hormone levels stabilize or decrease during the first 30 days after ^{131}I therapy. (*J Clin Endocrinol Metab* 84: 4012-4016, 1999)

GRAVES' DISEASE is the most common cause of hyperthyroidism in adults aged 20-50 yr (1). Radioactive iodine has been widely used for treatment of Graves' hyperthyroidism, and its efficacy, safety, and low cost have made it the preferred treatment for this disorder (2). Exacerbation of hyperthyroidism, observed in some patients after radioiodine therapy, has been attributed to follicular disruption followed by radiation damage, with subsequent leakage of the preformed thyroid hormone into the circulation (3). Because antithyroid drugs block thyroid hormone synthesis, it is thought that patients should receive methimazole or propylthiouracil before radioiodine dosing to deplete thyroid hormone stores and decrease radioiodine therapy hazards. Nevertheless, few studies have assessed the efficacy of this approach, which may represent an unnecessary increase in treatment risk and costs. Moreover, antithyroid drug therapy has been associated with relative radioresistance and with a decrease in radioiodine therapy effectiveness (4).

Few studies have focused on short term serum thyroid hormone changes after radioiodine administration. The accumulated data show conflicting results. Some studies report short term elevation in thyroid hormone levels (5, 6), whereas others report no changes (7, 8) or a decrease in thyroid hor-

mon levels after radioiodine therapy (9, 10). None of those studies has examined the relative effects of pretreatment with antithyroid drugs on the short term biochemical course after radioiodine administration.

The role of pretreatment with antithyroid drugs was recently addressed by Burch *et al.* (11), who reported a transient increase in thyroid hormone levels after interruption of drug treatment for radioiodine therapy, with no further increase in hormone levels after radioiodine administration. Those researchers have also shown that serum thyroid hormone levels decrease after radioiodine therapy without pretreatment with antithyroid drugs. However, that study did not follow a randomized control design, and only four patients were assigned to radioiodine therapy without pretreatment with antithyroid drugs.

Radioactive iodine therapy without pretreatment with antithyroid drugs may be a safe, effective, and less expensive alternative to treat Graves' hyperthyroidism. Therefore, the present randomized, prospective study was designed to evaluate the effect of pretreatment with antithyroid drugs on short term thyroid hormone levels after radioiodine therapy in Graves' hyperthyroidism.

Subjects and Methods

Subjects

The study was carried out between February 1997 and August 1998. Consecutive patients with a recent diagnosis of Graves' disease attending the Endocrine Division at Hospital de Clínicas de Porto Alegre were eligible. Graves' hyperthyroidism was diagnosed on the basis of suppressed TSH levels by sensitive assay, elevated serum thyroid hormone levels and 24-h radioiodine uptake, and detectable levels of antibodies against the TSH receptor. Exclusion criteria were previous treatment with radioiodine or thyroidectomy, signs of moderate or severe oph-

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thalmopathy (proptosis >22 mm, ophthalmoplegia, chemosis, or lagophthalmos), severe heart disease (symptomatic coronary heart disease, class III heart failure, New York Heart Association criteria), debilitating conditions, and large and compressive goiters (>150 g). Patients previously treated with antithyroid drugs whose treatment had been interrupted at least 3 months before the study were included.

Sixty patients were enrolled. Five patients were lost to follow-up; 1 was excluded because of pregnancy, and 3 patients did not achieve biochemical euthyroidism after treatment with methimazole. Thus, 51 patients participated in the study.

During the enrollment period the patients underwent a complete physical examination, including ocular examination and electrocardiogram. Data about duration of the disease, previous antithyroid drug therapy, and history of smoking were recorded, and thyroid volume was assessed by ultrasound. The study protocol was approved by the ethics committee at the Hospital, and all patients gave their informed written consent.

Treatment protocol and serial evaluation

Patients were randomly assigned to receive radioiodine therapy alone (28 patients) or pretreatment with antithyroid drugs plus radioiodine therapy (23 patients). In the first group, on the day of treatment, patients received a dose of radioiodine (200 μCi/g thyroid tissue as estimated by ultrasound, corrected by 24-h radioiodine uptake). A clinical and laboratory assessment was performed on the day of treatment and on days 2, 5, 7, 14, 20, and 30 after treatment.

In the second group, patients were treated with methimazole (30 mg daily) until biochemical euthyroidism was achieved. Patients were considered to have reached euthyroidism when serum thyroid hormone levels were within the laboratory reference range. Antithyroid therapy was interrupted 4 days before patients were given radioiodine (radioiodine dose was calculated in the same way as for the first group, based on a second 24-h radioiodine uptake performed on the day of treatment). A clinical and laboratory assessment was carried out on days 4 and 1 before radioiodine therapy, on the day of treatment, and on days 2, 5, 7, 14, 20, and 30 after radioiodine therapy.

Clinical evaluations were always performed by the same physician, who did not know whether the patient had received methimazole. To evaluate the degree of thyrotoxicosis, Wayne's questionnaire was employed (euthyroidism, ≤10; suspicion of hyperthyroidism, 11–19; hyperthyroidism, ≥20) (12). After radioiodine administration, symptoms and signs of thyrotoxicosis were graded according to Wayne's therapy index (12). Serum levels of T₄, free T₄ (FT₄), and T₃ were measured every morning on days scheduled for clinical and laboratory assessment, as described above. None of the patients received antithyroid drug therapy during the 30 days after radioiodine therapy. The β-adrenergic blocking agent propranolol (40–120 mg/day) was given to patients when tachycardia was more than 120 beats/min.

Serum hormone measurements

Assays were performed on batched serum samples (duplicates) that had been stored at –20 C pending study completion. Serum T₄ and T₃ levels were measured using RIA (Diagnostic Products, Los Angeles, CA; Immunotech, Marseille, France), and serum FT₄ was measured using Coat-a-Count assay (Immunotech, Marseille, France). Intraassay coefficients of variation were as follows: T₄, 3–8%; T₃, 7–10%; and FT₄, 3–6%. For values in the hyperthyroid ranges, intraassay coefficients of variation were the following: T₄, 6–9%; T₃, 6–12%; and FT₄, 4–8%. Interassay coefficients of variation were as follows: T₄, 10%; T₃, 12%; and FT₄, 7%. TSH was measured with a double antibody-sensitive assay (Immulite, Diagnostic Products). Plasma levels of TSH antibodies were determined by radioreceptor assay (CIS-Bio International, Cardiff, France). Reference ranges for each of these assays are shown in Table 1.

Statistical analysis

Baseline clinical and laboratory characteristics of the two groups of patients were compared using the χ² test or Fisher's exact test for qualitative variables or using Student's *t* test or Mann-Whitney's *U* test for quantitative variables. In each group, the variation of Wayne's therapy index and thyroid hormone levels over time was assessed by ANOVA

TABLE 1. Baseline characteristics of the two groups of patients with Graves' hyperthyroidism

	Radioiodine group (n = 28)	Methimazole-radioiodine group (n = 23)
Age (yr)	34.5 ± 7.8	37.6 ± 7.8
Sex (M/F)	4/24	2/23
Smokers (n)	13	9
Body mass index (kg/m ²)	22.0 ± 3.2	23.0 ± 4.1
Range of disease duration (months)	7 (1–72)	12 (1–120)
Wayne's clinical index ^a	24.3 ± 9.1	22.8 ± 6.9
Thyroid vol (mL) ^b	38.1 ± 18.2	32.4 ± 15.0
24-h radioiodine uptake (%) ^c	74.9 ± 17.4	71.8 ± 23.5
T ₄ (μg/dL)	22.7 ± 9.6	23.6 ± 5.8
Free T ₄ (ng/dL)	4.6 ± 0.46	4.8 ± 0.40
T ₃ (ng/dL)	476.8 ± 213.9	444.5 ± 195.1
TSH conc. (μIU/mL)	<0.03	<0.03
TRAb (U/L)	68 (10–944)	68 (6.1–275)

Values shown represent the mean ± SD or median (range). The reference ranges for laboratory values are as follows: T₄, 4.5–12.5 μg/dL (56.3–160.9 nmol/L); free T₄, 0.6–1.8 ng/dL (8.4–23.2 pmol/L); T₃, 78–182 ng/dL (1.19–2.8 nmol/L); and TSH, 0.4–4.5 mIU/L. Normal values for TSH receptor antibody are less than 11 U/L. To convert T₄ values to nanomoles per L and free T₄ values to picomoles per L, multiply by 12.87. To convert T₃ values to nanomoles per L, multiply by 0.01536. All *P* values for comparisons between groups were 0.05 or more.

^a Euthyroidism index, ≤10; suspicion of hyperthyroidism, 11–19; hyperthyroidism, ≥20.

^b Thyroid volume was measured by ultrasonography.

^c Iodine uptake was measured 24 h after the oral administration of 5 μCi (200 kBq) ¹³¹I and expressed as a percentage of the administered dose. The reference values are 15–35%.

by repeated measures (Friedman's test), followed by Dunnett's test. The correlation between changes in therapy index and serum thyroid hormone levels over time was assessed using Spearman's rank correlation procedure. *P* < 0.05 was considered statistically significant. The Statistical Package for Social Science 7.5 professional software (SPSS, Inc., Chicago, IL) was used for statistical analysis.

Results

Study population

The characteristics of the 51 patients with Graves' hyperthyroidism who were randomly assigned to receive radioactive iodine alone or radioactive iodine plus treatment with antithyroid drug are shown in Table 1. There were no significant differences between the 2 groups with respect to any of the characteristics listed.

Patient follow-up

The median for the period of time required to achieve biochemical euthyroidism in the group of patients pretreated with antithyroid drugs was 12 weeks (2–48 weeks). The mean number of medical visits was significantly higher in this group (3 ± 1 vs. 12 ± 4; *P* < 0.001). The 24-h radioiodine uptake determined 4 days after stopping methimazole in pretreated group was not different from that before treatment (78% vs. 72%; *P* = 0.589). The mean given dose of radioiodine (10.4 ± 5.4 vs. 8.2 ± 3.9) and the number of patients using propranolol (three vs. two) and/or oral contraceptive (eight vs. eight) were similar in both groups. Methimazole was replaced by propylthiouracil (300 mg/day) in three patients who developed rash or pruritus.

In the group of patients treated with radioiodine alone, a significant improvement was observed as early as 2 days after radioiodine therapy. The group of patients pretreated with antithyroid drugs experienced significant improvement of signs and symptoms after biochemical euthyroidism was achieved, whereas no other changes were observed either during preparation for radioiodine therapy or after therapy, as assessed by the Wayne's therapy index questionnaire (Fig. 1).

Changes in serum thyroid hormone levels

In patients who did not receive pretreatment, we observed mean increases of 5% and 9% in serum T_4 and FT_4 levels, respectively, on day 2 (Fig. 2), but these were not statistically significant upon *post-hoc* testing. A subsequent decrease in mean serum T_4 (25.4 to 22.5 $\mu\text{g/dL}$; 13%), FT_4 (4.5 to 3.8 ng/dL ; 15%), and T_3 (533.9 to 435.6 ng/dL ; 18%) levels occurred as early as 5 days after radioiodine administration. The decrease in serum T_4 levels was not statistically significant compared to day of treatment values; however, this decrease was significant compared to day 2 values ($P < 0.01$). Serum T_4 and FT_4 levels did not change between days 5 and 30, whereas the mean serum T_3 levels continued to drop, reaching the lowest value on day 30 (332.8 ng/dL ; $P < 0.01$; an additional decrease of 24%).

In the group of patients who received pretreatment with methimazole, the mean serum T_4 and FT_4 levels increased from 8.9 to 12.3 $\mu\text{g/dL}$ (38%) and from 1.4 to 1.9 ng/dL (an

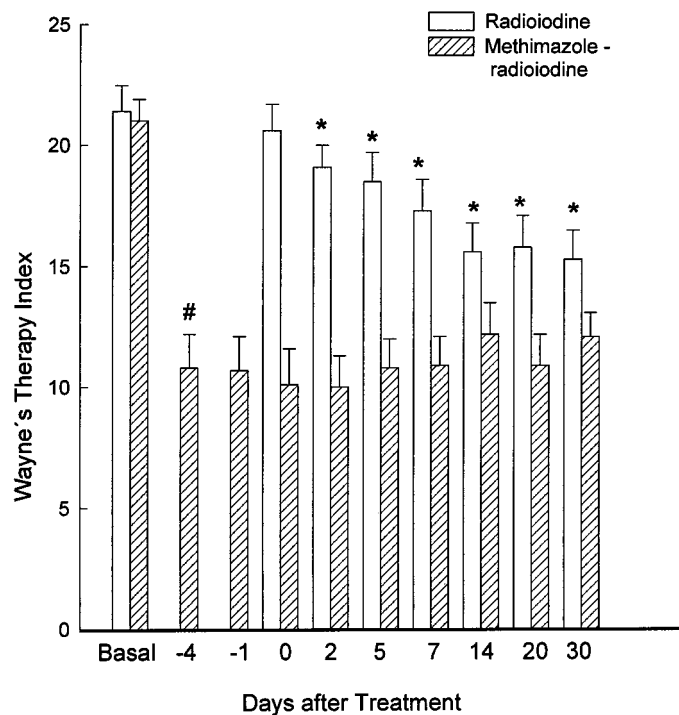


FIG. 1. Changes in the Wayne therapy index in patients with Graves' hyperthyroidism who were treated with radioiodine or methimazole-radioiodine. Negative numbers indicate days before treatment. *, $P < 0.05$ for the comparison with the value on the day of radioiodine administration (day 0). #, $P < 0.001$ for the comparison with the pretreatment value (basal).

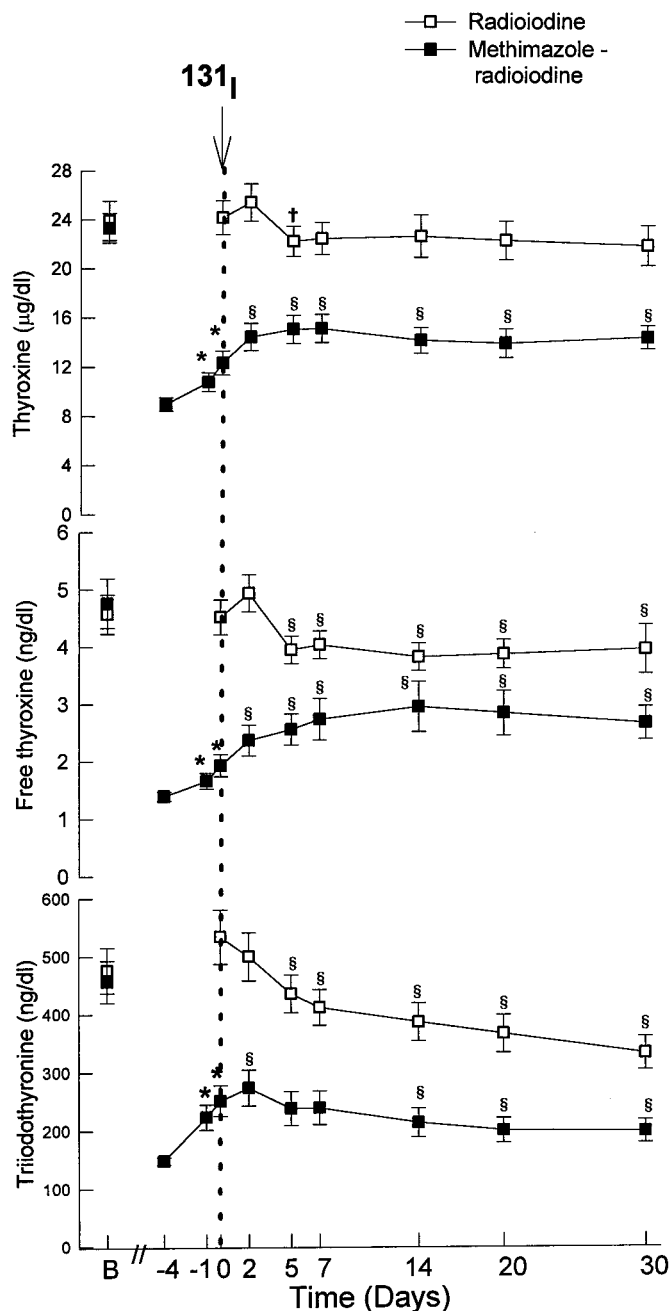


FIG. 2. Changes in thyroid hormone levels in patients with Graves' hyperthyroidism who were treated with radioiodine or methimazole-radioiodine. Negative numbers indicate days before treatment. *, $P < 0.01$ for the comparison with the value on the day the drugs were interrupted (day -4). †, $P < 0.05$ for the comparison with the value on day 2 after radioiodine administration. §, $P < 0.01$ for the comparison with the value on the day of radioiodine administration (day 0).

increase of 39%), respectively, after drugs were discontinued and before radioiodine administration (Fig. 2). An additional significant increase occurred in both hormone fractions after radioiodine ablation; serum T_4 levels reached the highest value on day 7 (15.1 $\mu\text{g/dL}$; $P < 0.01$; an increase of 23% compared to day of treatment value and of 70% compared to baseline value). Serum FT_4 levels reached the highest value

on day 14 (2.9 ng/dL; an increase of 36% compared to day of treatment value and of 107% compared to baseline value). Mean serum T₃ levels increased from 147.7 to 251.2 ng/dL (an increase of 70%) after antithyroid drug discontinuation and before radioiodine therapy. An additional increase of 9% in serum T₃ levels, from 251.2 to 273.5 ng/dL, was observed on the second day after radioiodine administration ($P < 0.01$; 85% compared to the baseline), followed by a progressive decrease from day 14 (213.3 ng/dL; $P < 0.01$; decrease of 15%) to day 30 (197.9 ng/dL; $P < 0.01$; decrease of 21%).

To determine whether changes in serum thyroid hormone levels after radioiodine administration would be different in patients with large goiters, we analyzed the results in seven patients with estimated thyroid size greater than 50 g (60.3 ± 12.2) in the nonpretreated group. In this subgroup, the variation in mean serum T₄, FT₄, and T₃ levels after radioiodine therapy displayed an identical pattern to that in the whole group, although statistical significance was achieved only for the decrease in serum FT₄ levels on day 30 (4.6 to 2.4 ng/dL; $P < 0.05$; decrease of 91%; results not shown).

For individual analysis of serum thyroid hormone changes, we considered that increases greater than 2 times the assay variation were significant. We identified a progressive increase in serum thyroid hormone levels after radioiodine dosing in two patients from the group receiving radioiodine alone (serum T₄: day 0, 13.5 and 28.9 μg/dL; day 30, 19.5 and 46.9 μg/dL, respectively; serum T₃: day 0, 184.9 and 370.4 ng/dL; day 30, 481.8 and 735 ng/dL, respectively). In the pretreated group, three patients coursed with steady increase in serum thyroid hormone levels after radioiodine administration, as follows: serum T₄: day 0, 8.6, 13.3, and 9.9 μg/dL; day 30, 17.0, 18.6, and 18.8 μg/dL, respectively; serum T₃: day 0, 127.6, 212.2, and 156.9 ng/dL; day 30, 254.6, 330.1, and 297.5 ng/dL, respectively. All patients present maximal serum thyroid hormone levels on day 30. We did not identify any special aspect of disease presentation in any of these patients. One of them, the subject with highest thyroid hormone levels, developed atrial fibrillation on day 30 that was promptly reversed by propranolol administration.

Correlational analysis showed that the changes in therapy index over time in patients receiving only radioiodine were positively correlated with the changes in mean serum FT₄ ($r = 0.823$; $P = 0.014$) and T₃ levels ($r = 0.937$; $P < 0.000$). The correlation between serum T₄ levels and Wayne's therapy index was not statistically significant ($r = 0.577$; $P = 0.150$).

Discussion

Our data demonstrate that thyroid hormone levels stabilize or decrease after radioactive iodine therapy in patients with Graves' hyperthyroidism who are not pretreated with antithyroid drugs. Accordingly, systematic clinical evaluations performed on the same days, such as biochemical measurements, showed improvement of the signs and symptoms of hyperthyroidism, and correlational analysis revealed that serum T₃ levels displayed an impressive direct correlation with therapy index, providing the best correlation to clinical manifestations. In pretreated patients, interruption of antithyroid drugs for radioiodine administration caused a significant increase in serum T₄, FT₄, and T₃ levels.

The practice of prescribing antithyroid drugs before radioiodine therapy began soon after clinical observations of worsening of hyperthyroidism shortly after radioiodine treatment (13). In fact, Larsen (14) observed a reduction in glandular T₄ concentration in patients treated with antithyroid drugs before surgery compared with that in nonpretreated patients. However, the exact frequency of clinically significant worsening of hyperthyroidism after radioiodine therapy is unknown, and it varies from series to series (3); similarly, studies dealing with changes in serum thyroid hormone after radioiodine treatment show conflicting results (5–10).

Recently, Burch *et al.* (11) suggested that short term increases in thyroid hormone levels after radioiodine therapy could be caused by discontinuation of drug therapy, rather than by radioiodine treatment itself. Those researchers observed a deterioration in thyroid function in a group of 17 patients immediately after interruption of drug treatment and before radioiodine dosing. Because that study did not look for biochemical euthyroidism in all patients before iodine administration, one could speculate that the increase in thyroid hormone levels occurred mainly in patients whose hyperthyroidism was not controlled (15). The results of this study, in which biochemical euthyroidism was required before radioiodine therapy, confirm those described by Burch *et al.* (11) and clearly demonstrate that drug discontinuation caused a significant increase in serum thyroid hormone levels even in euthyroid patients. An interesting observation was that despite the additional increment in thyroid hormone levels after radioiodine treatment, stability or decrease occurred after 7–14 days of radioiodine ablation, indicating that in most patients it is not necessary to reintroduce drug therapy, at least during the first 30 days after radioiodine administration.

Another major issue is whether pretreatment with antithyroid drugs will alter thyroid hormone levels after radioactive iodine therapy. We found that pretreatment with methimazole has little or no influence on thyroid hormone levels after radioiodine therapy, except for the effects of drug discontinuation described previously. The major difference observed between the groups was in terms of the rate of decrease in T₃ levels, which could be explained in part by the more rapid clearance in hyperthyroid patients. Radioiodine may cause follicular disruption followed by hormone leakage into the circulation (16), as shown by the slight increase in T₄ and FT₄ levels 2 days after radioiodine administration in nonpretreated patients. However, the subsequent decrease in hormone levels suggests either that the follicular cell is rapidly repaired or that the store of hormone is already depleted in a highly stimulated gland.

The greater magnitude of the acute decrease in circulating T₃ in response to radioiodine compared with the decrease in T₄ and FT₄ could be due to an effect of radioiodine on thyroidal T₃ production. The disproportionate increase in T₃ production in Graves' disease is well known, and it has been attributed to both the increase in the T₃ to T₄ ratio in Graves' thyroglobulin (17) and to high type 1 deiodinase levels in the gland (18). The recent finding of large amounts of type 2 deiodinase in Graves' thyroid suggests that the conversion of T₄ into T₃ may have an important role in T₃ overproduction

(19). As radioiodine therapy causes cell damage, a possible explanation for the acute decline in serum T_3 levels could be loss of deiodinase activity in the thyroid gland. In this study, the T_3 to T_4 ratio in nonpretreated patients decreased from 20.6 on the treatment day to 15.2 on day 30. The faster decrease in serum T_3 levels was also observed by Burch *et al.* (11), who suggested a direct effect on thyroid secretion and/or decreased T_4 availability for peripheral conversion to T_3 .

Two previous studies have reported an increase in serum thyroid hormone levels after radioiodine therapy (5, 6). We do not have an explanation for the difference between those results and our results, except that the studies had a different design and included patients with different causes of hyperthyroidism. Furthermore, individual analysis of thyroid hormone changes is complicated, because it is difficult to determine whether hormone variation originates from the disease itself, whether it is a result of assay variation, or whether it is induced by treatment. In our study, we identified 2 patients in the nonpretreated group whose serum thyroid hormone levels increased after radioiodine administration. Several noteworthy inferences originate from this observation. As the increase in serum thyroid hormone was progressive, reaching the highest level after the 10- to 14-day interval in which radioiodine thyroiditis is believed to peak (20), it is possible that this increase reflects treatment failure rather than a direct radioiodine effect; in fact, these 2 patients were the only ones, among 28 patients, who did not present a decrease in serum T_3 levels after radioiodine dosing. The speculation that patients with large goiter would be at higher risk for worsening of hyperthyroidism was not supported by the analysis of thyroid hormone changes in our subgroup of 7 nonpretreated patients with goiter greater than 50 g.

As expected, isolated radioiodine therapy did not control the hyperthyroid state during the 30-day observation period, indicating that pretreatment with antithyroid drugs should be considered when a faster biochemical euthyroidism is required.

In conclusion, we have demonstrated that short term increase in thyroid hormone levels in patients with Graves' hyperthyroidism receiving radioiodine treatment occurs mainly as a result of discontinuing antithyroid drug therapy. Among patients who receive radioiodine therapy without pretreatment, serum thyroid hormone levels will not change or decrease in the 30-day interval after radioiodine administration. We postulate that radioactive iodine therapy without pretreatment with antithyroid drugs can be safely pre-

scribed for most patients with hyperthyroidism associated with Graves' disease.

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