

# Thyroid-hormone Concentrations after Radiolodine Therapy for Hyperthyroidism

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*Fourteen hyperthyroid patients (11 men, three women), ages 28–66, were followed with serial measurements of serum thyroid hormone levels for 1 mo after therapy with I-131. Twelve patients had diffuse toxic goiters (25–70 g in size); two patients had multinodular glands (40–100 g). The patients were taking no antithyroid medications; ten patients were treated with propranolol. All patients received the equivalent of 5000 rad, except the two with multinodular glands, who received larger doses. There was no consistent pattern of serum  $T_4$  and  $T_3$  levels after the I-131 therapy. For the entire group, there was no significant increase of the mean serum hormone concentration. One group (three patients) had a mean  $T_4$  increase of 28% and a  $T_3$  increase of 91% above baseline at Days 10–11. Seven patients had minimal increases of hormone levels at Days 2–3, and a third group (four patients) had no increase of thyroid hormones after I-131 therapy. The patients with no rise in hormone concentrations had smaller goiters than the other groups. There was no correlation of the dose of radioactive iodine, or of the initial hormone concentration, with the rises or declines of  $T_4$  and  $T_3$  levels after I-131 therapy. Radioiodine therapy caused no significant increase of serum  $T_4$  and  $T_3$  concentrations in the majority of patients.*

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The use of radioiodine as an effective mode of therapy of hyperthyroidism is increasing. There have been several case reports of thyroid storm occurring 3–20 days after administration of I-131 for thyrotoxicosis (1–3). The clinical exacerbations of hyperthyroidism generally have been noted in elderly patients with multinodular glands, underlying cardiac disease, and debilitated physical condition. Recently, hyperthyroid patients have been studied for short intervals after radioactive iodine

therapy to examine acute changes in serum thyroid-hormone concentrations; increments of  $T_3$  and  $T_4$  levels were found 24–48 hr after treatment with I-131 (4,5). The present study provides a longer followup of hyperthyroid patients to examine possible increases of thyroid-hormone concentrations for 1 mo after treatment with radioiodine.

## METHODS

Fourteen hyperthyroid patients (11 men, three women), ages 28–66, were treated with I-131. Before treatment, the patients had increased levels of serum  $T_4$ , free  $T_4$  index ( $FT_4I$ ) and/or increased  $T_3$ ,

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and free T<sub>3</sub> index (FT<sub>3</sub>I), with suppressed serum TSH levels and clinical evidence of hyperthyroidism. When antithyroid medications had been administered, they were discontinued for at least 1 mo before I-131 treatment. Table 1 shows the thyroid weights, I-131 doses, and the baseline and maximum serum T<sub>3</sub> and T<sub>4</sub> concentrations. Twelve patients had diffuse toxic goiters ranging in size from 25 to 70 g. Two patients had multinodular glands (40 and 100 g). Ten patients were treated with propranolol to control tachycardia before treatment, and the same dose was continued throughout the study. The doses of propranolol were 10–30 mg four times daily; one patient (No. 9) received 40 mg every 4 hr. All patients received a dose of I-131 calculated to deliver 5000 rads to the thyroid, except the two patients with multinodular glands who received about 15,000 and 25,000 rads. The doses were determined by the weight of the gland based on planimetry of the thyroid scan, the 24-hr radioiodine uptake, and the effective half-time of the retained tracer dose (6).

The serum T<sub>3</sub> and T<sub>4</sub> concentrations were determined by radioimmunoassay (7). The normal T<sub>4</sub> is  $7.2 \pm 1.7$  (s.d.)  $\mu\text{g/dl}$  and the normal T<sub>3</sub> is  $152 \pm 32$  ng/dl. The T<sub>3</sub> talc uptake (T<sub>3</sub>U) was determined by the method of Parslow et al. (8), and free T<sub>4</sub> and free T<sub>3</sub> indices were calculated from the product of the serum T<sub>4</sub> and T<sub>3</sub> levels and the T<sub>3</sub>U. Although Patients Nos. 5, 6, and 9 had levels of T<sub>4</sub> in the upper normal range, their FT<sub>4</sub>I were elevated and they had elevated serum T<sub>3</sub> concentrations and sup-

pressed TSH levels. All serums from each patient were run in the same assay.

Baseline serum samples were obtained for 1–3 days before radioiodine treatment, then samples were obtained daily for the first week of therapy, and then three times weekly for three additional weeks. The blood was drawn at approximately the same time of day after the patient had been lying or sitting for 5 min to avoid positional changes that could influence thyroid hormone levels. The patients were examined nearly every day their bloods were drawn. The examination included a brief review of systems, vital signs, and physical examination, with emphasis on signs or symptoms of hyperthyroidism or thyroiditis. All subjects were studied through Day 13. Blood samples were not obtained for the entire month in Patients Nos. 1 and 10, who stopped their participation at Days 13 and 14. The study was discontinued at Days 15 and 17 in Patients Nos. 5 and 7 because of exacerbation of chronic obstructive lung disease. Patient No. 2, who was unable to take propranolol, had increased symptoms of hyperthyroidism at Day 18, and his study was discontinued at that point. Patients Nos. 8 and 12 were unable to have blood drawn on Days 1–3.

Analysis of the results was performed using paired and unpaired t-tests.

## RESULTS

There was no consistent pattern of serum T<sub>4</sub> and

TABLE 1. THYROID SIZE, I-131 DOSE, BASELINE AND MAXIMUM T<sub>4</sub> AND T<sub>3</sub> CONCENTRATIONS, AND DAY OF MAXIMUM HORMONE CONCENTRATIONS

	Patient No.	Thyroid size (g)	Dose rads/mCi	Baseline T <sub>4</sub> $\mu\text{g/dl}$	Maximum T <sub>4</sub> $\mu\text{g/dl}$	Day	Base line T <sub>3</sub> ng/dl	Maximum T <sub>3</sub> ng/dl	Day
<i>Group A</i>									
	1	70	5000/9	22.4	33.5	10	663	1246	10
	2	60	5000/15.1	13.3	17.3	18	247	400	11
	3	40	5000/5.1	26.2	31.7	6	460	1103	11
<i>Group B</i>									
	4	Multinodular 40	25000/100	10.1	12.5	3	241	286	2
	5	Multinodular 100	15000/100	10.7	13.4	3	212	278	3
	6	45	5000/4.3	19.3	24.8	20	365	449	9
	7	40	5000/4.1	15.0	19.2	17	270	345	16
	8	60	5000/6.4	9.4	11.6	25	238	293	25
	9	55	5000/5.5	17.2	20.7	7	951	1140	3
	10	40	5000/6	13.0	14.5	1	373	465	1
<i>Group C</i>									
	11	30	5000/25	21.9	No increase		487	No increase	
	12	30	5000/5.2	14.3	15.2	6	492	No increase	
	13	25	5000/4.2	12.1	No increase		205	226	1
	14	25	5000/2	20.8	22.2	1	699	717	1

T<sub>3</sub> after radioiodine therapy. In examining the entire group, serum T<sub>4</sub> and T<sub>3</sub> concentrations did not increase significantly, but changes of thyroid hormone concentrations after radioiodine varied greatly between individuals. Figure 1 shows that serum T<sub>4</sub> concentrations were relatively stable until Day 10, and thereafter declined gradually. There were minimal increases of serum T<sub>4</sub> at Days 3 and 8-10. Serum T<sub>3</sub> rose minimally at Day 3, and the mean peak levels occurred on Days 8-10 (9.5% above baseline,  $p > 0.5$ ).

The patients were divided into three groups: Group A—large increase of hormone levels (individual increases greater than 30% above baseline); Group B—slight increase (individual increases of 10-30% above baseline); and Group C—no increase (or individual increases of less than 10%). Table 1 shows the thyroid weights, doses of I-131, baseline and peak T<sub>3</sub> and T<sub>4</sub> concentrations. Figures 2 and 3 show the responses of the three groups. Group A consisted of three patients who had a mean increase of T<sub>4</sub> of 28%, and a 91% increase of T<sub>3</sub>, above baseline at Days 10-11. Only one patient (No. 2) had increased symptoms of hyperthyroidism with this rise of hormone level.

Of the seven patients in Group B, four had increases of hormone concentrations at Days 1-3, whereas three had increases at Days 9-25. As

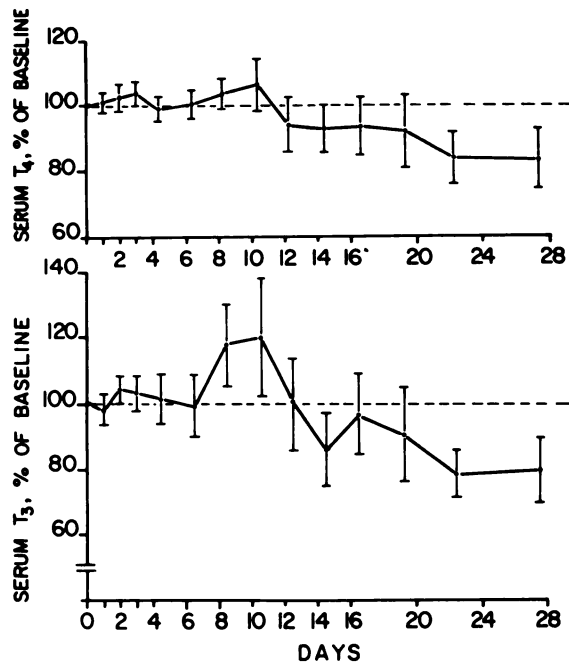


FIG. 1. Mean serum T<sub>3</sub> and T<sub>4</sub>, expressed as percentage of baseline  $\pm$  s.e.m., for entire group (N = 14), followed for 28 days after radioiodine therapy. Not all patients were sampled at each point. No point was significantly different from baseline.

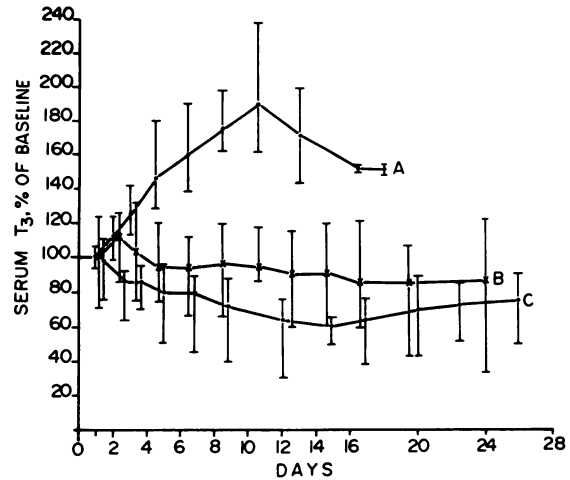


FIG. 2. Mean and range of serum T<sub>3</sub>, expressed as percentage of baseline, for Group A (three patients), Group B (seven patients), and Group C (four patients) followed for 28 days after I-131 therapy. Not all patients were sampled at each point.

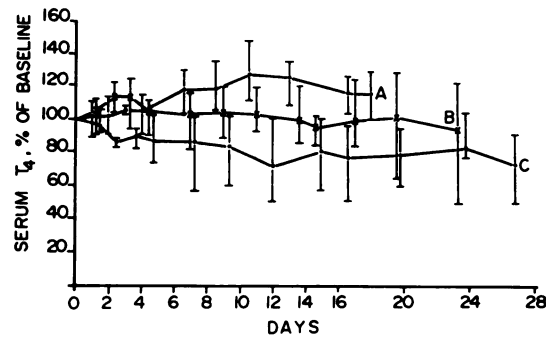


FIG. 3. Mean and range of serum T<sub>4</sub>, expressed as percentage of baseline, for Group A (three patients), Group B (seven patients), and Group C (four patients) followed for 28 days after I-131 therapy. Not all patients were sampled at each point.

shown in Figs. 2 and 3, the maximum mean T<sub>4</sub> rise was 12.2% at Day 3 ( $p < 0.05$  compared with baseline), and the maximum mean T<sub>3</sub> increment was 11.7% ( $p > 0.05$ ) at Day 2. Group C included four patients; their mean T<sub>3</sub> and T<sub>4</sub> levels declined throughout the month of study.

The patients of Group C had the smallest goiters (25-30 g) compared with the glands of Groups A and B (40-100 g; Tables 1 and 2). The mean thyroid size in Group C was significantly smaller than in the other two groups.

Table 2 shows that there was no relation between the initial thyroid hormone levels and the magnitude of increase of serum T<sub>3</sub> and T<sub>4</sub> concentrations after radioiodine therapy. The differences of baseline

**TABLE 2. THE MEAN (AND RANGE) THYROID WEIGHT AND BASELINE THYROID HORMONE CONCENTRATIONS FOR EACH GROUP**

	Group A (n = 3)	Group B (n = 7)	Group C (n = 4)
Thyroid weight (g)	56.7 (40-70)	56.7 (40-100)	27.5* (25-30)
Baseline T <sub>4</sub> (μg/dl)	20.6 (13.8-26.2)	13.5 (9.4-19.3)	17.3 (12.1-21.9)
Baseline T <sub>3</sub> (ng/dl)	455 (247-663)	378 (205-699)	471 (212-951)

\* P < 0.025 compared with Group A, P < 0.05 compared with Group B.

hormone concentrations between the groups were not significant. There was no correlation between the dose of I-131 and the rises or declines of hormone levels. The two patients who received 100 mCi I-131 had maximum increases of T<sub>4</sub> of 25% above baseline at Day 3 and a maximum increase of T<sub>3</sub> of 19% and 13% on Days 2-3.

Clinically most patients showed no exacerbation of hyperthyroidism, but a majority of them were treated with propranolol, making evaluation of symptoms difficult. No patient developed pain or tenderness of the thyroid, and with the exception of the three patients described below, no subject had increased tachycardia, tremor, diaphoresis, or other clinical evidence of worsening hyperthyroidism. The three exceptions were not treated with propranolol. One subject (No. 2) developed tachycardia, increased tremor, and diaphoresis at Day 18, coincident with increased T<sub>4</sub> concentration. Patients Nos. 5 and 7 had exacerbations of chronic obstructive lung disease, with increased dyspnea, tachycardia, and deterioration of arterial blood gases. However, only Patient No. 7 had serum T<sub>4</sub> and T<sub>3</sub> concentrations increased above baseline. In Patient No. 5 the thyroid hormone concentrations were below baseline.

#### DISCUSSION

Studies describing exacerbations of hyperthyroidism and thyroid storm after radioactive iodine did not follow thyroid hormone concentrations closely after the therapy (1-3). Maloof et al. (9) made frequent determinations of protein-bound iodine (PBI) levels over a 30-day period in nine patients treated with I-131. His results were similar to ours; two patients had a marked increase of PBI levels at 10-15 days and the remainder had no PBI increase. He found no relation between exacerbations of hyperthyroidism and the PBI levels; however, the PBI determinations may have reflected release of iodoproteins, in addition to T<sub>4</sub>, from the damaged gland. More recent studies have shown acute release of thyroid hormone 24-48 hr after radioiodine therapy. Shafer et al. (4) studied 13 thyrotoxic patients for 4 days after I-131 therapy. They found a significant increase of both T<sub>3</sub> (46%

above baseline) and T<sub>4</sub> (19% rise) at 24-48 hr after therapy. The patients received a mean dose of 8000 rads. By 72-96 hr, the hormone values had returned to baseline. Creutzig et al. (5) reported a 7-day followup of 46 patients treated with 7000 rads for diffuse toxic goiters. No significant increase of T<sub>4</sub> was noted, whereas the T<sub>3</sub> levels rose by 9-16% the first day after treatment. By Day 7 all values were lower than baseline. On the other hand, Wise et al. (10) studied five patients for 3 days after receiving ablative doses of I-131 for thyrotoxicosis, and all patients had significant lowering of T<sub>3</sub> levels by Day 3. Recently, Schimmel and Utiger (11) found no significant increase of serum T<sub>4</sub> and T<sub>3</sub> concentrations in eight patients studied daily for 10 days after I-131 treatment with 7000 rads. There was a minimal initial rise of serum T<sub>3</sub> at Day 2, then a fall to a nadir below baseline values, at Day 8.

In the present study we found no consistent effect of radioiodine on thyroid-hormone concentrations. In contrast to the previous reports (4,5), the mean increases of T<sub>4</sub> and T<sub>3</sub> levels were not significant, possibly because of the large variation between individuals and the difficulty in obtaining samples over the entire 4 weeks in all subjects. The patients appeared to respond in three different ways to radioiodine therapy: a small, early increase of thyroid hormone; a delayed, greater rise of hormone; or no increase of hormone concentration. Group B, seven patients, showed a small rise of mean hormone concentration at Days 2-3, similar to the time course described by others (4,5). Group A, three patients, had marked increases of hormone concentration at Days 10-11, corresponding to the clinical exacerbations described in earlier case reports (1-3), reflecting the acute effect of the increased serum T<sub>3</sub> concentrations (12). On the other hand, Group C, representing 31% of the patients, had no increase of mean hormone levels, as has been reported recently (11). In the present study, clinical exacerbations were difficult to detect, perhaps because of the propranolol therapy. However, only two patients (one from Group A, one from B), who were not treated with propranolol, had worsening of their clinical status coincident with increasing thyroid hormone concentrations after the first week. Per-

haps the other subjects were protected symptomatically by propranolol therapy. The effect of propranolol in lowering the serum  $T_3$  concentrations could not be excluded (13).

In each group in the present study, the rise and fall of serum  $T_3$  and  $T_4$  levels paralleled one another. This suggests that release of both  $T_3$  and  $T_4$  from the damaged gland may be one of the causes of the exacerbation of hyperthyroidism after I-131 therapy. The patients with the smallest glands had minimal or no increase in thyroid hormone concentrations after I-131, which suggests a relationship between size and thyroid-hormone release. On the other hand, there appeared to be no relation between the dose of I-131 or the initial  $T_3$  and  $T_4$  values and the rise in serum  $T_3$  and  $T_4$  concentrations after I-131 therapy. The therapeutic doses of I-131 in the present series were lower than the doses administered in the earlier studies (4,5,9-11).

In summary, no significant increases of  $T_3$  and  $T_4$  concentrations were noted when the group is taken as a whole. However, there appeared to be three different responses following I-131 therapy: a delayed but great increase; an early but slight increase; and no increase in thyroid-hormone concentrations. A majority of the patients showed no increase. However, because about one-third of our patients (3) had large hormone increases at Day 10 or 11, we recommend that patients be observed carefully for exacerbation of hyperthyroidism for the first 2 weeks following I-131 therapy.

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