THERAPEUTIC NUCLEAR MEDICINE

Simultaneous Treatment of Toxic Diffuse Goiter with I-131 and Antithyroid Drugs: A Prospective Study

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We report a prospective study to evaluate the effect of antithyroid drugs containing the sulfhydryl radical on the outcome of I-131 (RAI) therapy.

Twenty-four male patients with toxic diffuse goiter were assigned randomly into two treatment groups: Group A received RAI treatment while on antithyroid drugs after attainment of euthyroidism; Group B received no antithyroid drugs before, or when, RAI was given. Patients in each group received a dose of RAI calculated to deliver approximately 5000 rads per treatment.

The incidence of hypothyroidism at 12 mo was 8% for Group A and 36% for Group B ($p < 0.01$). During 12–102 mo of follow-up, no additional hypothyroidism was encountered in Group A. Two patients with significantly elevated TSH levels were found in Group B, one at 20 mo and one at 75 mo after RAI. The mean time to cure was 15.2 ± 9.1 mo for Group A and 19.7 ± 8.2 mo for Group B (NS: $p > 0.45$).

The improved therapeutic outcome of patients in Group A suggests that further validation of the method in a larger patient population, including females, is warranted.

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Hypothyroidism was recognized as a major undesirable side effect of radioactive iodine (RAI) treatment as early as 1946 (*1*); 33 yr later, it still remains the major drawback of this therapeutic approach.

Many dosage schedules of RAI have been proposed and tried. These range from arbitrary deliberate ablation (*2*) to elaborately calculated doses (*3–5*). To date, a method of determining the precise dose that will consistently restore the hyperthyroid patient to euthyroidism has not been devised. While it is possible to deliver a relatively accurate radiation dose to the thyroid, the biological response of the gland remains unpredictable.

The administration of antithyroid drugs just before RAI treatment has been shown to increase the radioresistance of the thyroid to RAI (*6–9*). This protection from the effects of ionizing radiation is thought to be conveyed by the sulfhydryl radical (*6,10,11*), since drugs not containing this group do not exhibit this effect (*12*). Regardless of the type of antithyroid drug used, it has been routine practice to discontinue all antithyroid medication 3–4 days before RAI administration.

The present study was undertaken to evaluate the effect of RAI treatment while patients with toxic diffuse goiter continue to take antithyroid medication. It is proposed that sulfhydryl-containing antithyroid medication, by increasing thyroid resistance to ionizing radiation, will make the therapeutic response to RAI less variable. By calculating the administered dose while patients are stabilized on the drug, one can also eliminate the altered iodine kinetics that occur when the drug is withdrawn just before RAI treatment.

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MATERIAL AND METHODS

Male patients with confirmed toxic diffuse goiter were assigned by a random process into two radioactive iodine

TABLE 1. GROUP A: RAI ADMINISTRATION CONCOMMITANTLY WITH ANTITHYROID DRUGS

	Age at onset	% Uptake	$t_{1/2}$ eff (days)	Calc. dose rads	Dose mCi	Total mo on PTU	Mo on PTU before RAI	Mo from RAI to cure	Mo after cure	Mo RAI to hypothyroidism	Present TSH μIU/ml
					Euthyroid, one treatment						
DW	43	22.7	3.7	5000	18.2	11	4	7	89	—	6
RM	45	25.5	4.6	5000	10	31	12	20	55	—	4.4
DH	34	23.5	3	5000	40	24	7	17	65	—	2.4
JA	51	32	7.2	5000	18	17	3	14	92	—	3.2
RC	56	49	5.7	5000	14.4	27	7	20	88	—	1.6
RB	43	28.9	5.4	6000	10.7	6	5	4	102	—	3.2
RM	21	34.7	6	5000	6.9	12	8	4	12	—	2.1
RJ	58	43	6.2	5000	6.5	13	5	8	17	—	3.1
					Euthyroid, two treatments						
EA	52	55	5.2	5000	18		6				
		33	8	5000	22	24	—	18	50	—	NA
LM	24	51.6	3.5	1900	8.9		8				
		37.6	5.5	5000	16	21	—	20	60	—	7.2
					Hypothyroid						
EW	54	25	2.8	5000	30	8	4	—	—	4	—
					Status pending						
RT*	28	20	6.2	5000	6.5		12				
RG	58	45	4.8	5000	12.1		9				
		19.4	6.5	5000	15.4						

* Received Tapazole.

(RAI) treatment groups: Group A with antithyroid drugs; Group B without them. Included in this report are all patients assigned to protocol between 1969 and 1977 who were at least 12 mo post-RAI administration at the time of the report.

Treatment protocol. *Group A.* Patients in this group (Table 1) were rendered euthyroid with antithyroid drugs before RAI administration. Propylthiouracil (PTU) and methimazole were used in this study. (Both contain sulfhydryl radicals.) The I-131 dose was calculated and administered while patients were stable on maintenance doses of antithyroid medication. The latter was then slowly tapered off and discontinued, guided by history and by physical and laboratory findings.

Group B. Patients assigned to this control group were treated with RAI without pretreatment with antithyroid drugs. In seven out of 11 patients in whom rapid alleviation of hyperthyroidism was deemed necessary, PTU was administered 7–10 days *following* RAI treatment (Table 2). These were then tapered off and discontinued as in Group A. Thus this control group of patients differs from those in Group A in not receiving antithyroid drugs before and at the time of RAI treatment.

Dose calculation. The dose of I-131 was determined using the modified formula of Marinelli, Quimby and Hine (*4,5*) as follows:

$$\frac{5000 \times T_{1/2}(\text{I-131}) \times \text{thyroid wt.} \times 100}{120 \text{ rads}/\mu\text{Ci} \times t_{1/2}\text{eff} \times \% \text{ uptake} \times 1000} = \text{mCi I-131}$$

The radiation dose delivered to the thyroid was approximately 5000 rads in both groups of patients.

The thyroid weight was estimated from the thyroid scan using the Bauer-Blahd formula (*3,5*):

$$\text{Area (cm}^2\text{)} \times \text{avg. length (cm)} \times 0.321 = \text{g thyroid}$$

Effective half-life was measured in each patient after a diagnostic dose of I-131 was given for measurement of thyroidal uptake.

Time to cure. Euthyroidism was determined in both groups on the basis of clinical findings and laboratory tests, including T_4RIA, T_3RIA, RT_3U, and TSH. The time of cure was based on the earliest documented euthyroid date (without antithyroid drugs) that could be confirmed on subsequent 6-mo examinations.

RESULTS

There was a total of 30 patients initially admitted to protocol. The results obtained on 24 are reported here.

TABLE 2. GROUP B: RAI ADMINISTRATION WITHOUT ANTITHYROID DRUGS

	Age at onset	% uptake	$t_{1/2}$ eff (days)	Dose rads	Dose mCi	Mo from RAI to cure	Mo after cure	Mo RAI to hypothyroidism	PTU after RAI	Present TSH μIU/ml
					Euthyroid, one treatment					
JB	54	45	8	5000	22	27	41	—	Yes	<2
VC	54	55.9	8	5000	14.1	20	45	—	Yes	1.8
RK	23	76	6.7	5000	4.4	3	75	—	Yes	7.5
JP	24	49	5.7	5000	9.2	3	48	—	No	NA
					Euthyroid, two treatments					
CS	43	47	5.9	5000	7.8				Yes	
		24	5.9	5000	10.1	17	20	—		13*
JW	66	49	5.9	5000	5.3				Yes	
		27	6.3	5000	8.5	21	39	—		61.6*
					Hypothyroid					
PB	33	66.4	6.1	5000	5.1			5	No	
WC	55	53	6.2	5000	9.7			10	No	
McD	57	17.2	6.5	5000	16			5	No	
WO	68	42.4	6	5000	7.9				Yes	
			NA	2500	4.2			11		
					Status pending					
LP	54	53	6.1	5000	5.8				Yes	

* TSH >3 s.d. above mean

Not included are four protocol failures in Group A (two for noncompliance; one for thyroid surgery; and one for spontaneous remission) and two protocol failures in Group B (one death from unrelated cause; and one lost to follow-up). The results are tabulated in Tables 1 to 4.

There were 13 patients in Group A (Table 1) and 11 in Group B (Table 2). The mean age at onset of patients in Group A was 43.6 ± 12.5 (range 21–58 yr) and that of Group B was 48.3 ± 14.8 (range 23–66 yr). These two means are not statistically different ($p > 0.44$).* The percentage of radioiodine uptake for Group A was 34.1 ± 11.6 and for Group B 45.7 ± 6.4 ($p > 0.5$). The effective $t_{1/2}$ (days) for the diagnostic RAI dose was 5.1 ± 1.9 for Group A and 6.4 ± 0.8 for Group B ($p > 0.5$). (See also Tables 1 and 2).

All patients received a dose calculated to deliver 5000 rads to the thyroid each treatment. (Exceptions are patients RB and LM in Group A and patient WO in Group B, whose doses were found to be in error.) The mean mCi dose of I-131 per treatment for Group A was 15.8 ± 9 (range 6.5–40) and for Group B 9.2 ± 5 (range 4.2–22). Corresponding average rad doses were 4868 for Group A and 4821 for Group B (Table 3).

In Group A there were ten patients who were cured (two requiring a second therapy dose), comprising 76.9% of total patients treated in this group (Table 3). The time from initial diagnosis to cure was 19.7 ± 8.2 mo, 6.5 ± 2.5 mo before RAI therapy, and 13.2 ± 6.7 mo after (Table 4). The time of observation after date of cure ranged from 12 to 102 mo (mean 63 ± 31). All patients had T_4RIA, T_3RIA, RT_3U, and clinical examinations done intermittently during this follow-up period. All were within normal range. TSH testing done at the time

TABLE 3. AVERAGE I-131 DOSE PER TREATMENT AND RESPONSE TO THERAPY

	Total No. patients	Avg. dose per treatment (mCi)	Avg. rads dose	Euthyroid		Hypothyroid		Pending		Retreatment	
				No.	%	No.	%	No.	%	No.	%
Group A	13	15.8 ± 9	4868	10	76.9	1	8	2	15.4	3	23
Group B	11	9.2 ± 5	4821	6	54	4	36	1	9	3	29

TABLE 4. DURATION OF PTU TREATMENT AND TIME TO CURE

	Time diagnosis to cure	Time PTU before RAI	Time RAI to cure
Group A	19.7 ± 8.2	6.5 ± 2.5	13.2 ± 6.7
Group B	—	—	15.2 ± 9.1

of report had a mean value of 3.6 ± 1.8 μIU/ml.

There was one patient (8%) in Group A who became hypothyroid 4 mo after treatment (Table 3). Review of our records revealed that he was the first patient admitted to the study. He was hypothyroid by laboratory criteria at the time of RAI administration (T_4 = 4 μg%) and the calculated $t_{1/2}$ eff on PTU was considerably shorter than one determined a few weeks earlier. This may have contributed to the administration of a higher dose than needed (30 mCi).

Two patients in Group A were still borderline hyperthyroid at the time of this report, necessitating small doses of PTU (12 mo and 14 mo after treatment) (Table 1).

In Group B, six patients were cured (two requiring a second therapy dose), comprising 54% of all patients in this group (Table 3). The time from initial diagnosis to cure was 15.2 ± 9.1 mo. The time of observation after attainment of cure was 44.6 ± 17 mo (range 20–48 mo). All patients received the same laboratory and clinical examinations performed intermittently as those in Group A. Two patients (CS and JW) had highly elevated TSH levels (13 and 61.6 μIU/ml, respectively) at the time of this report (Table 1).

There were four patients (36%) in Group B who became frankly hypothyroid and required maintenance supplements of thyroid medication (Table 3). The incidence of hypothyroidism in this group was significantly higher than in Group A ($p < 0.01$). All four patients became hypothyroid within the first 12 mo (5–11 mo) after RAI treatment.

There was one patient in this group who was still borderline hyperthyroid at the time of report (16 mo after RAI treatment) (Table 2).

DISCUSSION

Many factors influence the radiation dose that RAI delivers to the thyroid gland. A number of studies have addressed themselves to manipulation of these factors without any significant alteration in the long-term results of therapy. It appears, therefore, that there may be great biological variability in the radiosensitivity of the thyroid to ionizing radiation delivered to it.

Although, to date, quantitation of this radiosensitivity is not possible, it has been shown that antithyroid drugs containing sulfhydryl radicals increase the resistance of tissues to ionizing radiation both in vivo and in vitro (*6–11*). We might expect, therefore, that if a patient is maintained at the euthyroid level with antithyroid drugs at the time of treatment, variations in radiosensitivity might be minimized and the outcome of therapy improved. The data presented in this report lend some support to this theory.

The control group in our series (Group B) shows results very similar to those reported for medium-dose regimens (*13–19*). The incidence of hypothyroidism is 35% at 1 yr, and 29% of the patients required retreatment. At the time of report, 54% of patients in this group were euthyroid, but when the data are closely examined, it is apparent that two additional patients (CS and JW) are good candidates for late development of hypothyroidism. Their TSH levels are significantly elevated, and although their thyroid hormone levels in the blood are still within the normal range, they have shown a continuous decline during the past year. These findings suggest that this group of patients will have the continuous yearly incidence of hypothyroidism expected with this form of therapy (*20–23*).

When patients were treated with RAI while maintained at euthyroidism with antithyroid drugs (Group A) the incidence of hypothyroidism was reduced to 8% in the first year, compared with 36% in Group B ($p < 0.01$). This rate (Group A) is comparable with that in the low-RAI-dosage regimens (*22–23*). It was achieved without excessive need for retreatment (23%) compared with the controls (29%) (Group B). None of the patients in this group has developed hypothyroidism after the first 12 mo posttherapy, and at the time of report (12–102 mo after therapy) none had laboratory evidence indicating incipient thyroid failure.

Time required for the thyrotoxic patient to achieve euthyroid status is an important consideration in the mode of therapy chosen. Cure with radioactive iodine cannot be achieved quickly. It is now fairly well accepted that high doses will achieve cure more rapidly than low doses, but this is offset by the greater incidence of hypothyroidism encountered with the higher doses. In our control group (B), the mean time to cure was 15.2 ± 9.1 months, apparently slightly shorter (not significant, $p > 0.27$) than in Group A, which took 19.7 ± 8.2 mo to cure. A portion of this time difference is accounted for by the 6.5 ± 2.5 mo during which the patients in Group A were being stabilized and maintained at euthyroidism on antithyroid drugs before administration of RAI. After RAI therapy, each group took approximately the same time to acheive cure (15.2 ± 9.1 mo Group B; 13.2 ± 6.7 mo Group A).

The data presented demonstrate that it is possible to treat male hyperthyroid patients and achieve a low rate of hypothyroidism without concomitant high retreat-

ment rates and excessive periods of hyperthyroidism. The slight prolongation of time to cure in the prepared groups might be economically disadvantageous. The need for patient compliance could also present a difficulty. However, the significant improvement in the outcome in the prepared group suggests that the method merits further study in a larger population, including female patients.

FOOTNOTE

* Statistical analysis, when indicated, was done using Student's t-test.

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