EARLY RESULTS OF ^{125}I THERAPY OF THYROTOXIC GRAVES' DISEASE

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In an attempt to reduce the high incidence of hypothyroidism following radioiodine treatment of Graves' disease, ^{125}I was used instead of ^{131}I. The low-energy emissions of ^{125}I theoretically deliver less radiation to the nucleus of the thyroid cell than to its hormone-generating apex. Sixty patients were treated with an estimated delivered "high" dose of 200 μCi/gm and forty with a "low" dose of 100 μCi/gm. After more than 12 months followup, 71% of the "high-dose" group were euthyroid, 24% still hyperthyroid but half of these substantially improved, and 5% hypothyroid. The "low-dose" treatment was a failure since 53% of the patients remained toxic. It is concluded that ^{125}I in the dose range of 200 μCi/gm is effective in controlling Graves' disease. Subsequent followup will reveal whether its use will reduce the incidence of late hypothyroidism.

The high cumulative incidence of late permanent hypothyroidism following treatment of Graves' disease with ^{131}I in conventional "7,000-rad" doses was first suspected by Werner (*1*), conclusively documented by Beling and Einhorn (*2*), and subsequently confirmed by numerous authors. It represents a major undesirable effect of this treatment modality. "Low-dose" ("3,500-rad") ^{131}I treatment reduces the frequency of hypothyroidism (*3*) but is less successful in bringing the toxic symptoms under control initially. In an attempt to find an effective method of radioiodine treatment which does not cause late hypothyroidism in a large number of patients, several groups of investigators have used ^{125}I (*4–6*). This approach is based on the hypothesis that the low-energy conversion and Auger electrons emitted by ^{125}I with their minimal tissue penetrance will have a much higher radiation effect on the hormone-forming apical portion of the thyroid cell than on the nucleus which is felt to be responsible for cell survival and replication (*7,8*).

Successful control of hyperthyroidism with ^{125}I was reported from Scotland where dietary iodine intake is low (*4*) whereas the preliminary studies from Israel (*5*) and New York and Amsterdam (*6*) would indicate that the response to ^{125}I might be different in areas of high iodine intake.

METHODS

Patient selection. All patients were selected from the in-patient and out-patient services of the LAC-USC Medical Center. Any patient with the usual clinical and laboratory evidence of hyperthyroid Graves' disease who ordinarily would have been treated with ^{131}I was given ^{125}I. Individuals previously treated with ^{131}I or surgery and those with multinodular goiters or solitary toxic nodules were excluded. Patients with moderate-to-severe manifestations were rendered euthyroid with thioamide drugs before radioiodine therapy. Individuals with mild clinical hyperthyroidism were given radioactive iodine without pretreatment.

Calculation of ^{125}I dose and method of administration. The amount of ^{125}I to be administered was calculated from the gland size estimated by palpation and the 24-hr radioactive iodine uptake measured with ^{131}I immediately before treatment to achieve consistency within our patient group and to be able to compare dose ranges within our series and with those of other investigators (see Table 3). The patients were divided into two groups:

1. Group A (high dose): The first 60 patients were given 200 μCi/gm of estimated thyroid

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weight retained as indicated by the 24-hr uptake, i.e.:

$$\frac{200 \times \text{gm} \times 100}{\text{RAIU \%}} = \mu\text{Ci } ^{125}\text{I administered.}$$

2. Group B: The following 40 patients were given 100 μCi/gm of estimated thyroid weight retained as indicated by the 24-hr uptake, i.e.:

$$\frac{100 \times \text{gm} \times 100}{\text{RAIU \%}} = \mu\text{Ci } ^{125}\text{I administered.}$$

The value of 200 μCi/gm retained was chosen for Group A because Greig's groups had reported promising results in their early communication (*9*) when they gave twice the amount of ^{125}I they would have used with ^{131}I.

Followup. All patients were followed in the Thyroid Clinic of the LAC-USC Medical Center and seen by the same investigator every 2 weeks. On each visit, a clinical and laboratory evaluation was made, including hemoglobin, white cell count, serum thyroxine by competitive protein-binding assay, and serum T_3 resin uptake. When clear symptoms of thyrotoxicosis recurred, thioamide drugs were promptly started. Reinstituted thioamide treatment was gradually withdrawn again after several months, and the patients were observed closely for signs of recurring toxicity.

RESULTS

The response to ^{125}I therapy in the two treatment groups is tabulated in Tables 1 and 2. Of the 60 patients in Group A (Table 1), 42 were followed effectively for a minimum of 12 months. The mean total administered dose to this group was 22 mCi with a range of 6–60 mCi. Thirty patients or 71% of Group A became euthyroid with a mean response time of 14 weeks. Nine patients or 21% exhibited transient clinical and laboratory evidence of hypothyroidism which eventually remitted to a euthyroid state. Ten patients or 24% of Group A remained toxic for 12 months after therapy. In four of these, there was marked improvement in the disease and they are currently asymptomatic but cannot be classified as euthyroid because of persistent mild elevation of laboratory indices. Four others are under control on thioamides. Two patients were retreated 12 months after the first ^{125}I therapy and became euthyroid, but the results of the second treatment are not included in this analysis. Two patients, or 5% of Group A, developed persistent hypothyroidism 16 and 40 weeks after ^{125}I treatment, respectively*.

Treatment results in Group B are summarized in Table 2. Of the total of 40 patients, 28 were followed

* This was documented by both a low free thyroxine and elevated immunoassayable TSH value initially and 6 months later after withdrawal of thyroid hormone therapy.

TABLE 1. RESULTS OF ^{125}I-TREATMENT OF GRAVES' DISEASE (200 μCi/GM) (GROUP A)

	Number of patients	% pre-treated	Estimated gland size (gm ± s.d.) (range)	% 24 hr RAIU ± s.d. (range)	Number Sex	Mean age ± s.d. (range)	Mean dose mCi ± s.d. (range)
	42 (100%)	47	59 ± 20.9 (25–100)	66 ± 21.5 (24–98)	6 M 36 F	41 ± 13.7 (18–63)	22 ± 9.4 (6–60)
Euthyroid	30 (71%)	47	57 ± 20.4	63 ± 23.7	3 M 27 F	43 ± 13.5	19 ± 6.8
Hyperthyroid	10 (24%)	50	59 ± 23.8	77 ± 8.6	3 M 7 F	39 ± 12.6	19 ± 8.0
Hypothyroid	2 (5%)	50	60 ; 80	56 ; 65	2 F	20 ; 38	19 ; 28

TABLE 2. RESULTS OF ^{125}I-TREATMENT OF GRAVES' DISEASE (100 μCi/GM) (GROUP B)

	Number of patients	% pre-treated	Estimated gland size (gm ± s.d.) (range)	% 24 hr RAIU ± s.d. (range)	Number Sex	Mean age ± s.d. (range)	Mean dose mCi ± s.d. (range)
	28	93	62 ± 19 (30–100)	75 ± 16 (33–100)	7 M 21 F	41 ± 15 (21–60)	10 ± 5.6 (28–32)
Euthyroid	12 (43%)	83	60 ± 23	72 ± 14	4 M 8 F	42 ± 17	9 ± 4.1
Hyperthyroid	15 (53%)	100	63 ± 18	78 ± 17	3 M 12 F	44 ± 14	10.8 ± 6.8
Hypothyroid	1 (4%)	100	75	78	1 F	52	10

TABLE 3. SUMMARY OF PUBLISHED EXPERIENCE WITH ^{125}I

Author	Number of patients	Dose (μCi/gm) administered/ delivered	Responses (%)		
			Euthyroid	Thyrotoxic	Hypothyroid
Lewitus (5)	45	2.5 mCi	42	51	7
Lewitus (5)	11	4–6 mCi	54	37	9
Werner (6)	13	310/200	85	0	15
McDougall (4)	15	1,008/675	66	7	27
McDougall (4)	77	589/365	69	5	23
McDougall (4)	56	382/240	80 (64%)*	7 (23%)*	13
Siemsen	42	300/200	71	24	5
Siemsen	28	140/100	43	53	4

* Corrected for retreatment.

effectively for a minimum of 9 months. Only 12 patients, or 43% of Group B, became euthyroid with a mean response time of 18 weeks. Of the nonresponsive group of 15 patients or 53%, 6 are kept on thioamides while 9 are tolerating very mild disease mainly manifested by abnormal laboratory data. One patient became and remained hypothyroid.

There was no discernible difference between Groups A and B in regard to radioactive iodine uptake values, sex, age, size of gland, severity of disease, and pretreatment with thioamide. No patients developed nodules in the thyroid gland. Those who are still significantly thyrotoxic are being retreated with a similar dose of ^{125}I.

DISCUSSION

The immediate goal of studying the therapeutic use of ^{125}I is the selection of a dose which yields prompt control of thyrotoxicosis while avoiding a prohibitively high initial incidence of hypothyroidism. If the basic rationale of differential distribution is correct, one might then expect a lower incidence of late hypothyroidism with such a dose.

The search for optimal dose of ^{125}I has been approached by various investigators in different ways. Greig's group (*4*) in Scotland started with very large amounts of ^{125}I and empirically lowered the dose to a range comparable with ours. Lewitus, et al (*5*) in Israel, on the other hand, based on the same general theory but on somewhat different dose calculations, started with very small doses and empirically increased them in subsequent series. Since they still found a high incidence of recurrence with total doses of 4–6 mCi of ^{125}I, they have recently tried a combination of ^{125}I and ^{131}I.

Geographic differences in dietary iodine intake may affect therapeutic results and make comparison between reports from various parts of the world difficult. Iodine intake is low in Scotland, high in Israel. Therefore, we considered it worthwhile to study ^{125}I treatment in a patient population with high dietary intake as in our area, using dose ranges comparable to those reported from Scotland.

Table 3 summarizes the results of the published experience with ^{125}I treatment. The dose regimens are somewhat difficult to compare since Lewitus, et al (*5*) used a standard dose, McDougall, et al (*4*) and Werner, et al (*6*) calculated the dose administered from the estimated gland weight alone whereas we took both gland weight and 24-hr radioiodine uptake into account. For the purposes of comparison, we have corrected, in the data from our own series, the average dose delivered to the average dose administered by multiplying by the average uptake. Conversely, for the data from McDougall's and Werner's series, we have converted the average dose administered to the average dose delivered by dividing by the average uptake. Both values are listed in Column 3 of Table 3. It can be seen that the dose ranges in our Group A and McDougall's Group 3 are very similar. The results are also very much alike if we correct the data in McDougall's Group 3 for the nine patients who were still thyrotoxic after the initial treatment dose and required retreatment with ^{125}I. This is remarkable in view of the different iodine intake.

McDougall, et al (*4*) found that the initial therapeutic response to doses two to three times that used in the present series (their Groups 1 and 2) was not significantly better than with lower doses but induced early permanent hypothyroidism in a large number of cases. On the other hand, doses of significantly less than 200 μCi/gm of gland delivered are associated with a high incidence of persistent thyrotoxicosis as indicated both in our Group B and in the reports by Lewitus, et al. Therefore it would appear that an estimated delivered dose of 200 μCi of ^{125}I/gm of gland is approximately optimal for initial control of thyrotoxicosis.

Whereas the fear of carcinogenic effects of ^{131}I used

for treatment of hyperthyroidism in adults had been dispelled by extensive statistical information (*9*), there is some concern about the carcinogenic potential of ^{125}I. Gross, et al (*10*) giving 100 female rats ^{125}I and ^{131}I in varying amounts found two animals that developed differentiated carcinoma in the ^{125}I-treated group and none in the ^{131}I-treated group. Whereas these data may not be relevant to human subjects, the possibility of tumor stimulation has to be kept in mind.

The basic rationale for using ^{125}I instead of ^{131}I in the treatment of hyperthyroid Graves' disease is the search for an agent that controls hyperthyroidism well without the high risk of late hypothyroidism. The major remaining question regarding usefulness of ^{125}I is then: is there any long-term cumulative incidence of hypothyroidism following ^{125}I therapy as is seen with ^{131}I treatment? This question can only be answered by adequate followup of all patients treated with this substance. We are carefully following this group of patients by periodic clinical examination and laboratory studies including T_4 assay and TSH radioimmunoassay. Some of the patients have now been followed for as much as 3 years and no significant changes have occurred in the results as shown in Table 1. It would appear that the initially favorable results reported in our study and by others (*4,5*) warrant further clinical trials, but these should be performed under carefully controlled conditions as an investigative form of therapy.

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