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CURRENT STATUS OF RADIOACTIVE IODINE TREATMENT OF HYPERTHYROIDISM

David V. Becker, M.D.



David V. Becker, M.D.
Professor of Medicine and Radiology,
Cornell University Medical College,
Director, Division of Nuclear Medicine
New York Hospital-Cornell Medical Center,
New York

Current evidence suggests strongly that the underlying defect in Graves' disease is an immunological abnormality and that the elevated levels of thyroid hormones are due to an autoimmune stimulator mechanism. As yet, this recent knowledge has had no impact on the management of hyperthyroidism and reliance must still be placed primarily on therapy directed at the thyroid gland to reduce its secretions and consequently the level of circulating thyroid hormones. The only "permanent" methods of treatment, radioactive iodine therapy and surgery, achieve this purpose by destroying or removing a substantial proportion of the thyroid follicular cells.

Surgery, which has been used for almost 80 years now, results in permanent cure of the disease in 85% of patients. Radioactive iodine (^{130}I) was first used to treat hyperthyroidism in the late 1930s, but only in the 1950s when ^{131}I became widely available was this radioisotope established as an effective agent to control hyperthyroidism. Today, ^{131}I is generally accepted as the treatment of choice for hyperthyroidism in most patients over age 30 and is preferred in patients of any age when hyperthyroidism is part of a complicated medical situation or after the failure of other therapeutic measures. Recently, there has been an increasing tendency to use radioactive iodine in patients between the ages of 21 and 30. In a few medical centers, it is even used in children, although this practice is not generally preferred

except under unusual circumstances. It is clearly contraindicated in pregnancy both because of the sensitivity of the fetus to radiation and because the fetal thyroid begins to accumulate iodine at about the 12th week.

When radioactive iodine was first introduced, serious concern about the possible hazards of therapy with radiation for benign disease led to the limitation of its use to patients over age 45. The primary concerns were its potential late carcinogenic effects on the thyroid and marrow. Since radiation was also recognized as a cause of genetic alterations in animals, its use in humans, initially at least, was limited to patients past the childbearing age. Considerable evidence now exists to reassure us about the safety of radioactive iodine treatment of hyperthyroidism.

Radioactive Iodine Therapy as a Possible Cause of Leukemia

Early studies on the effects of radiation demonstrated that large external doses of ionizing radiation (more than 50 rads) lead to an increase in the incidence of leukemia in human populations, with a peak about six years after exposure.^{1,2} An average dose of radioactive iodine for the treatment of hyperthyroidism delivers 8 to 16 rads to the blood.³ Since some patients require multiple doses, they may receive considerably more blood radiation.

In 1961, the US Public Health Service Cooperative Thyrotoxicosis Follow-up Study was initiated. Its primary objective was to test for an increase in the incidence of leukemia

in hyperthyroid patients treated by radioactive iodine as compared to hyperthyroid patients treated by other means.⁴ In this project, 36,000 hyperthyroid patients from 26 medical centers were studied; more than 96% of the patients were later located and reexamined, with a mean follow-up of eight years. Twenty-two thousand of these patients were treated with radioactive iodine ¹³¹I, and 14,000 were treated surgically or with antithyroid drugs. The Table shows the adjusted rate of incidence of leukemia for two subgroups of these hyperthyroid patients, each followed up for more than 100,000 patient-years.⁴ No significant difference was found in the incidence of leukemia between the groups. Other studies have similarly shown no increase in leukemia following radioactive iodine treatment of hyperthyroidism.^{5,6}

Incidence of Thyroid Neoplasms Following Radioactive Iodine Therapy

Much evidence accumulated over the last 20 years has documented an increased incidence of thyroid neoplasia following thyroid radiation incidental to x-ray treatments of the head, neck, and chest areas in infants and children.⁷ External neck radiation, in doses as small as 6 rads but usually ranging from 100 to 500 rads, has been associated with the development of benign and malignant thyroid neoplasms, with a latent period of 5 to 35 years.^{8,9} However, no significant incidence of thyroid cancer has been found in adults treated for hyperthyroidism with external-beam x-ray therapy.¹⁰

Animal studies had previously demonstrated similar consequences from internally delivered thyroid radiation from iodine isotopes.^{11,12} Since the radiation from internally deposited radioactive iodine is not homogeneously distributed and delivered at much lower dose rates as compared to external x-radiation, some difference in effects might be expected and, indeed, has been found.

The Thyrotoxicosis Follow-up Study also examined the questions of whether the amounts of ¹³¹I used in the treatment of hyperthyroidism would cause an increase in the development of thyroid neoplasms.¹³ Eight thousand hyperthyroid patients had been treated surgically for Graves' disease; in this group, 32 unsuspected thyroid cancers were found, for an incidence of 3.8 per thousand. It was assumed that the rate of malignancy expected in the patients treated with radioactive iodine would be identical to that found at surgery. In fact, only nine malignant neoplasms were found in the group of 16,000 patients treated with radioactive iodine and followed up for a mean of eight years, an incidence of 0.56 per thousand. This is considerably fewer than

would have been expected based on the rate established in the surgically treated patients. On the basis of these and other data in the study, it was concluded that the risk of thyroid cancer in patients receiving ¹³¹I therapy for Graves' disease is negligible.

Since only a relatively small number of children have received radioactive iodine therapy for treatment of hyperthyroidism, only limited data on late effects are available. However, these suggest that individuals under the age of 20 at the time of therapy have no greater risk for the late development of thyroid cancer than do those who receive radioactive iodine therapy as adults. On the other hand, the risk of the late appearance of benign thyroid nodules after radioactive iodine exposure in children is greater than in adults.¹⁴ However, because of the long latent period of some of the late effects of radiation and the long lifetime anticipated for children, prudence and discretion in the use of radioactive iodine in younger age groups would seem advisable.

In summary, it appears from a number of studies that, following the usual therapeutic doses of radioactive iodine (5,000 to 10,000 rads), the incidence of thyroid cancer is, if anything, less than that in surgically treated patients.¹⁵ This is probably accounted for by the fact that these doses of radiation either destroy follicular cells outright or totally inhibit cell division, thus removing the thyroid's ability to respond to thyrotropin (TSH) stimulation in a manner likely to lead to malignant growth.¹⁵ This remains a hypothesis, but strongly suggests that it may be necessary to monitor more carefully the potential carcinogenicity of smaller therapeutic doses of radioactive iodine.

Possible Genetic Effects of Radioactive Iodine Therapy

Direct information on the possibility that radioactive iodine treatment of hyperthyroidism increases the risk of having a child with a harmful genetic trait is not available. Extrapolations based on a calculated radiation dose to the gonads, up to 17 rads, suggest that the maximum increased risk of having a child with a congenital abnormality after ¹³¹I treatment would be no more than 0.025% over and above the spontaneous incidence of such abnormalities of 0.8%.¹⁶ Recent work, however, suggests that the ovarian dose is considerably lower, approximately 0.3 rads/mCi of ¹³¹I administered.¹⁷ The average radioactive iodine dose for hyperthyroidism of 7 mCi would thus deliver about 2 rads to the ovaries. This radiation dose should be compared to the ovarian dose from common abdominal diagnostic radiographic procedures, such as the barium enema and the intravenous pyelogram, in which gonadal doses may range up to 1

Age-Adjusted Leukemia Rates Following Treatment of Hyperthyroidism With Radioactive Iodine and Surgery^{4*}

	No. of Patients	Patient-Years	Adjusted Rate of Leukemia, Cases/100,000 Patient-Yrs.	Standard Error of Rate
¹³¹ I	18,379	119,000	13	3.1
Surgery	10,731	114,000	16	4.0

*There were no significant differences for age, sex, or type of leukemia.

to 2 rads. Necessary abdominal diagnostic x-ray procedures are not withheld from young women because of possible genetic effects, and an even stronger case can be made for radioactive iodine therapy when possible alternatives are considered. However, it is important to be certain that patients receiving radioactive iodine therapy are not pregnant. Pregnancy testing should be considered in all women of childbearing age, especially as highly accurate and rapid pregnancy tests are now available. In addition, some may wish to limit radioactive iodine administration to the first two weeks of the menstrual cycle.

Studies reviewing children and adolescents treated for hyperthyroidism with radioactive iodine appear to show no harmful effects on fertility and birth history—even in individuals treated for thyroid cancer with much larger doses of radioactive iodine.¹⁸

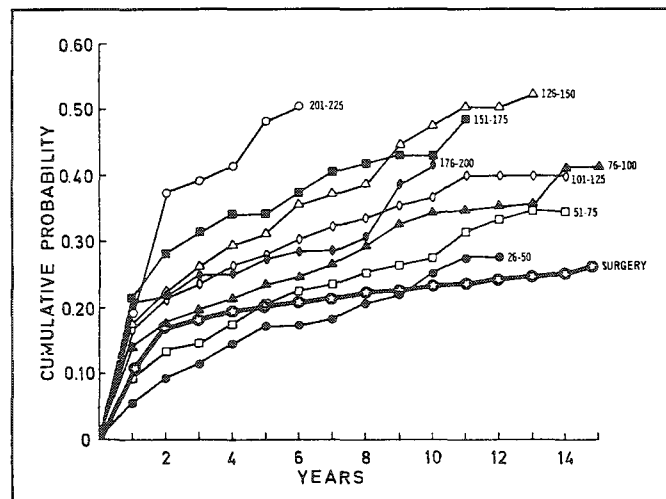
Hypothyroidism Following Radioactive Iodine Therapy

It was not until radioactive iodine therapy for hyperthyroidism had been in use for almost 15 years that it became apparent that a major consequence of this form of therapy was the induction of hypothyroidism in a large proportion of patients. In 1961, the first report was presented of a regular increment in the appearance of hypothyroidism after the first year, with a cumulative ten-year incidence of 26%.¹⁹ Subsequent studies by many investigators indicated that the occurrence of hypothyroidism ten years after treatment ranged from 40% upward.

The Thyrotoxicosis Follow-up Study represents the largest single study of late results of radioactive iodine treatment: 11,000 patients with Graves' disease who received radioactive iodine as their initial treatment (mean age at treatment, 49.7 years) were followed up for a mean period of 7.5 years.²⁰ At the end of the study, 59% were euthyroid, 35% were hypothyroid, and 6% had had a recurrence. A surgical group of 5,200 patients (mean age at treatment, 40 years) had a somewhat longer mean follow-up of 12.7 years. At termination of the study, 62% were euthyroid, 25% were hypothyroid, and 14% had had a recurrence.

The Figure, using standard life-table techniques, shows the probability of the development of hypothyroidism following different treatment doses of ¹³¹I delivered to the gland in a single administration.²⁰ This graph represents the outcome in 6,000 patients who had no prior treatment for hyperthyroidism before radioactive iodine and on whom the necessary data were available to calculate the dose delivered to the thyroid. In all groups, the annual probability of becoming hypothyroid is greatest in the first year, ranging from 6% for administered activity calculated to deliver less than 50 μ Ci/gm to 21% in patients receiving 176 to 200 μ Ci/gm. After the third year, there is a somewhat greater probability of becoming hypothyroid with amounts greater than 125 μ Ci/gm than with smaller doses, but in general the curves tend to be parallel. It has been suggested that the early-appearing hypothyroidism may be directly related to the radiation dose received by the thyroid, while that occurring after the first few years may be independent of dose and related instead to the pathophysiology of Graves' disease.²¹

Since the probability of developing hypothyroidism can be directly correlated with the radiation dose received by the



Cumulative probability of becoming hypothyroid following a single treatment with ¹³¹I, as determined by standard life-table techniques. Dose range of radioactive iodine indicated on each curve is given in microcuries per gram delivered to the thyroid. Heavy line indicates annual probability of becoming hypothyroid following surgical thyroidectomy. (Reproduced with permission from Becker et al²⁰).

thyroid,^{14, 15} it is appropriate that the major efforts to decrease the incidence of late hypothyroidism have been directed primarily to reduction of the administered radioactive iodine dose. A considerable number of studies concur in showing that a lower dose schedule does reduce the incidence of early hypothyroidism.²²⁻²⁴ However, this is usually achieved at the cost of larger numbers of inadequately treated patients who will often require both supplementary medication to control symptoms as well as retreatment with radioactive iodine. The duration of clinical disease requiring active medical management in these patients is thus considerably prolonged.

That factors other than size of dose may be involved is also suggested by studies indicating that the average dose in patients in whom myxedema developed was not significantly different from the average dose received by patients who remained euthyroid.^{25, 26} Unfortunately, adequate evaluation of varying dose strategies requires very long-term follow-up of large groups of patients; the natural and inevitable attrition of patient populations makes it difficult to obtain such data.

Because of the great variability in the results of radioactive iodine treatment and the inability to predict the outcome in any individual patient, there has been a tendency to accept hypothyroidism as inevitable. A natural extension of this view is the proposal that larger therapeutic doses be used to produce earlier and more certain control. Even deliberate thyroid ablation with immediate and permanent supplementation with thyroid hormones has been advocated.²⁷ However, the substitution of one disease for another on a casual basis seems an inappropriate response to our present difficulties in resolving some of the questions raised by this form of therapy.

Use of a variety of dose formulations and calculations does not appear to decrease the occurrence of late hypothyroidism. It is therefore not surprising that efforts at careful dosimetry have lost favor, since they demand extra effort from both physician and patient. However, since radioactive iodine has an established place among the therapeutic modalities available in Graves' disease, there should be room for further efforts to resolve this admittedly difficult problem.

Methodology of Radioactive Iodine Therapy

To evaluate the results of any therapeutic modality, it is important to define as precisely as possible the factors that may determine the outcome. For radioactive iodine treatment, the most important of these is the radiation dose received by the thyroid. All formulations for radiation therapy require certain information and certain assumptions for the calculation of the mean absorbed dose. These include (1) the mass of target tissue (thyroid weight), (2) the total activity retained (thyroidal radioactive iodine uptake of therapy dose), and (3) duration of activity in target tissue (biological half-life).

Other pertinent factors relate to the physical characteristics of the isotope used (half-life, type, number, and energy of particles emitted), which are constant for any isotope and need not be further considered here.

Some aspects of thyroid physiology introduce variability that cannot be readily quantitated or mathematically formulated in precise dosimetry calculations. Nonuniformity of distribution of isotope within the thyroid at a microscopic level is related to the degree of function of individual follicles and the degree of activity of the thyroid. These, and other factors even less well defined, probably account for what is called "radiation sensitivity."

The precise uptake of the administered dose and the biologic half-life differs from individual to individual and frequently from time to time in the same individual. Sometimes, unexpected differences appear between tracer and therapy dose in the same individual; the reasons for this are unclear, but there is a sufficient difference in about 15% of patients to require that the uptake of the therapeutic dose be specifically measured if one is to make a reasonable estimate of the radiation dose actually received by the thyroid.¹⁵ The correlation of end results with thyroidal radiation dose would appear to be the datum most essential to any efforts to improve the results of therapy.

The major effects of ¹³¹I on the thyroid are due to the beta rays this isotope emits, most of which are of relatively high energy. Because of this, the dosimetry formulations proposed by Snyder et al,²⁸ Quimby and Feitelberg,²⁹ and others will provide results identical for ¹³¹I to the absorbed fraction method described below.

Since the delivered radiation dose is the most important measurable factor in determining the outcome of therapy, it is appropriate to conceptualize treatment in terms of units of absorbed radiation, ie, rads. For routine clinical use, the calculation of dose can be readily simplified. Since many factors in dosimetry formulations for any particular radionuclide are constant (ie, physical half-life, spectrum, and energy of beta rays) or can be assumed to vary within a limited range (bio-

logic half-life), such factors can be combined. The Quimby and Feitelberg²⁹ formula is as follows:

Formula 1:

$$\text{Dose (rads)} = \frac{90 \times \mu\text{Ci Administered} \times 24\text{-Hour Uptake}}{\text{Gland Weight (gm)} \times 100}$$

The constant in the formula includes many factors, including an assumed biologic half-life of 24 days and appropriate physical constants. General experience suggests that a dose of between 5,000 and 7,000 rads is appropriate for the diffusely enlarged gland of Graves' disease. In terms of microcuries per gram delivered to the thyroid, the equivalent of this rad dose is 56 to 78 $\mu\text{Ci/gm}$.

Once a dose of millicuries per gram has been determined (Figure), the following simplified expression may be used: Formula 2:

$$\text{Administered Dose } (\mu\text{Ci}) = \frac{\mu\text{Ci/gm Desired} \times \text{Gland Weight}}{\% \text{ Uptake at 24 Hours}} \times 100$$

With some experience, the mass of the thyroid can be estimated by palpation. Such estimates, especially for smaller glands (under 50 gm), can probably be made within 10% to 20% of actual gland weight. Thyroid scanning may assist somewhat in this estimation, and it is likely that sonography will greatly improve the accuracy of such estimates. Thyroidal uptake of the therapy dose is a major factor in calculating radiation dose and can be measured quite precisely. On the other hand, the turnover of iodine by the thyroid (biologic half-life) is of less significance in most patients since the relatively short physical half-life of the isotope (eight days) minimizes the importance of variation of the usually longer biologic half-life of thyroidal radioactive iodine in hyperthyroid patients (which ranges from 10 to 30 days).

It has been noted that about 15% of hyperthyroid patients have a very rapid turnover of thyroidal radioactive iodine due to a relatively small pool of iodine in the thyroid. This situation, which often follows antithyroid drug administration, will significantly decrease the radiation received by the thyroid unless compensated for by increasing the administered dose³⁰. The "small pool syndrome," as it has been called, can be diagnosed by a few daily measurements of neck uptake or by the determination of the serum protein-bound ¹³¹I level at 24 hours (since blood levels of radioactivity are markedly elevated in this situation). Appropriate correction of the administered dose can be made by multiplying formula 2 by a factor $(0.75 + 6/\text{biologic half-life})$ incorporating the biologic half-life as measured from a pretherapy tracer study. Other dose formulations compensate for variations in thyroidal turnover rate by including a factor for the level of the protein-bound ¹³¹I in the dose formulation.³¹

Despite difficulty in accurately predicting the outcome of radioactive iodine therapy in a given individual, a number of variables have been shown to influence results. Men are less likely to have hypothyroidism than women; race is also a factor, since blacks appear to be more resistant to radioactive iodine.²⁰ Younger individuals appear to be more at risk for hypothyroidism. Larger thyroid glands appear to be more resistant, but also tend to have their weight underestimated. A nodular thyroid (nodular Graves' disease) is also more resistant and requires a larger dose. Environmental and geo-

graphic factors, possibly related to the iodine content of the diet, have also been implicated. Considerable data suggest that prior administration of antithyroid drugs increases the resistance of the gland to radioactive iodine, and it has been suggested that patients who are most severely hyperthyroid may be more resistant to radioactive iodine, possibly reflecting a rapid thyroidal turnover of ^{131}I .

Toxic nodular goiter (Plummer's disease), in which one or more autonomously hyperfunctioning nodules suppress the function of the rest of the gland, is particularly resistant to radioactive iodine and often requires doses two to three times larger than those given for toxic diffuse goiter (Graves' disease). Even at these large doses, it is relatively uncommon to induce hypothyroidism in this type of thyroid gland.

The Problem of Late Hypothyroidism

It seems likely that a substantial incidence of hypothyroidism will result from radioactive iodine therapy no matter what dose is used, and to date no effective way of predicting response in a given individual exists. The diagnosis of hypothyroidism and its management, while theoretically simple, is associated with a number of serious problems. In its mildest form, hypothyroidism is often difficult to diagnose, particularly if not considered among the diagnostic possibilities. Some laboratory tests have severe limitations in screening effectiveness. Low serum thyroxine levels are not uncommon in euthyroid radioactive iodine-treated patients, the metabolic difference apparently being made up by increased secretion of triiodothyronine. Serum TSH level, which has proved to be extremely sensitive in the diagnosis of spontaneous hypothyroidism, is not uncommonly elevated after radioactive iodine therapy even in patients who are apparently clinically euthyroid. This may suggest diminished thyroid reserve, but the question of whether all such patients should immediately be treated with supplemental thyroid has not been answered. In any event, careful lifetime follow-up of all treated hyperthyroid patients is of great importance.

Another major problem in the treatment of permanent hypothyroidism, as with many chronic diseases requiring medication, is drug compliance. Studies where careful follow-up has been done have shown that between 20% and 50% of hypothyroid patients given replacement therapy either were not taking the prescribed medication or were taking it in a different dose than that prescribed. The slow insidious onset of hypothyroidism, particularly in elderly people, is too easily accepted as part of the aging process, and the increasing fatigue and indolence only deepens the patients' apathy, decreasing the likelihood that they will return to their physicians.

Long-term follow-up by various direct means must be made to ensure that the patient and his family are aware of the necessity for maintaining lifelong contact with a physician. Follow-up registries, such as those established in Scotland, seem likely to eventually become an integral part of treatment management.³²

Summary

Evidence appears to have established the safety of radioactive iodine treatment of adult hyperthyroidism. Its advantages are its efficacy, simplicity, and relatively low cost. Its

major disadvantage is a high incidence of hypothyroidism, but the disadvantages of alternative forms of therapy appear to be at least as great. Radioactive iodine, as other methods of permanent therapy of hyperthyroidism, is unphysiologic in that it does not remove the causative mechanisms of the disease. Realistic recognition of its limitations and advantages is necessary for its satisfactory use.

To prescribe any drug mentioned in this article, the readers should consult full prescribing information.

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