Radioactive Iodine Treatment of Intractable Angina Pectoris

by

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INTRODUCTION

The use of radioactive iodine for the induction of hypothyroidism in euthyroid patients with intractable angina pectoris was first described in 1950 (1). Since that time, there have been numerous reports confirming the usefulness of this modality of treatment (2-11). Although no claims have been made for \(^{131}\)I therapy as to the effect on either mortality rates or the underlying pathologic process, worthwhile results have been cited in approximately 75 per cent of the cases treated. Despite the apparent unanimity of opinion on the efficacy of this form of therapy, there is considerable variation in the reports cited in dosage schedules employed and in the mode of assessment of the results of radioiodine treatment. This lack of uniformity suggested to us that although generally accepted, this therapeutic modality might merit periodic re-evaluation. We have, therefore, reviewed our experience with radioactive iodine treatment of angina pectoris over a nine year period with particular regard to: a) \(^{131}\)I dosage schedules, b) correlation of symptomatic relief of angina with induction of hypothyroidism, and c) the overall efficacy of this form of therapy.

CLINICAL MATERIAL AND METHODS

The case material was selected from a group of patients treated with radioactive iodine between November, 1954 and July, 1963. All presented with severe, incapacitating angina pectoris presumably due to arteriosclerotic coronary artery disease and their cardiac status clinically corresponded to New York Heart Association functional class III or IV (12). Angina was judged by the attending physician to be intractable and unresponsive to all other forms of medical therapy prior to referral to the Radioisotope Laboratory. Of a total of 80 patients treated during this nine year period, 48 patients met the following requirements for inclusion in this study: (1) a survival of not less than six months following \(^{131}\)I therapy, (2) a closely supervised clinical follow-up supplemented by appropriate laboratory data (plasma PBI, etc.) to ascertain: a) if significant improvement in angina had occurred, and b) whether or not the patients were rendered hypothyroid. These simple criteria allowed a reasonable evaluation of the efficacy of induced hypothyroidism in relieving anginal pain. The group consisted of 18 women and 30 men ranging in age from 34 to 82 years with a mean age of 59 years. No significant sex difference was noted in either baseline thyroid function studies, or the results of \(^{131}\)I therapy.

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No attempt was made in case selection to separate those patients on prior or ongoing anticoagulant therapy, nor was any attempt made to evaluate the possible contributory role of other forms of medical therapy in the amelioration of angina after radioiodine treatment. The clinical impression of a euthyroid state was confirmed prior to $^{131}$I therapy by the determination of 24-hour thyroidal radioiodine uptake and plasma PBI. The 24-hour $^{131}$I uptake exceeded 20 per cent in all but three patients and was not a factor in the selection of dosage schedule(s). The original policy of the laboratory was to attempt to render the patient hypothyroid with a single large dose of $^{131}$I. Subsequently, in an attempt to obviate the risk of inducing radiation thyroiditis with transient hyperthyroidism, the radioactive iodine was administered in three equally divided doses at weekly intervals (vide infra). After therapy, the patients were followed at three-monthly intervals during the first year and thereafter twice yearly by their private physicians as well as by the examining physician in the Radioisotope Laboratory. Repeat $^{131}$I uptakes and plasma PBI's were obtained at intervals in the follow-up period. The final evaluation in February, 1964 was based on these records and was supplemented by questionnaires submitted to the attending physicians. The follow-up period ranged from a minimum of six months to a maximum of 78 months with an average follow-up period of 25 months.

The diagnosis of $^{131}$I-induced hypothyroidism was based on: (1) Definite signs and symptoms of hypothyroidism, confirmed clinically by the private physician and/or ourselves and (2) a plasma PBI level persistently below 3.5 $\mu$ gm per cent (the lower limit of normal in our laboratory). The majority of patients met both criteria although a small number of patients who were judged to be clinically hypothyroid did not have a plasma PBI determination following therapy.\(^1\) The post-therapy results were classified simply as "improved" or "not improved". The minimal criterion for inclusion in the former group was a definite reduction in the frequency of anginal attacks with no change in level of activity and ranged all the way to complete absence of angina pectoris at full activity. The patients were considered to be "not improved" if improvement was not maintained for a minimum of six months following $^{131}$I therapy.

Once hypothyroidism was induced, the patients were given small doses of thyroid extract (10-45 mg) sufficient to ameliorate the uncomfortable symptoms of hypothyroidism without producing exacerbation of angina.

RESULTS

As noted earlier, no sex difference was observed in relation to baseline $^{131}$I uptakes, therapeutic dose of $^{131}$I, improvement in symptomatology, etc. The patient population was divided into two groups following therapy: those in whom hypothyroidism was induced, and those who remained euthyroid. The efficacy of therapy in these two groups is summarized in Table I.

\(^1\)Although post-therapy $^{131}$I uptakes were obtained in many of the patients studied, we have not utilized this datum as an independent criterion for induced hypothyroidism. We have seen several patients who remained clinically euthyroid with normal plasma PBI levels in whom the post-therapy uptake was depressed significantly below normal.
The case material was also divided into single and multiple dose groups and these results are illustrated in Figure I.

Fourteen of the 16 patients treated with a single dose of $^{131}I$ (87 per cent) were rendered hypothyroid. Twenty-five of 32 patients (78 per cent) were rendered hypothyroid after a multiple dose course of therapy; however, six of these 25 patients required varying additional doses of $^{131}I$ before hypothyroidism was induced. One patient required three full courses of therapy with a total dose of 150 mc before hypothyroidism and improvement of angina was achieved.

No significant difference in mean age (58 years), baseline $^{131}I$ uptake (28 per cent) or total therapeutic dose (single dose 18 mc–multiple dose 58 mc) was noted between the nine patients who remained euthyroid and those in whom hypothyroidism was induced. The former were followed in the Radioisotope Laboratory for an average of 17 months post therapy, and the persistence of a euthyroid state was documented by conventional clinical and laboratory criteria. Despite the apparent refractoriness to $^{131}I$ ablative therapy, six of these nine patients were judged to have had significant improvement in anginal symptoms.

Three of the patients receiving single dose therapy developed mild radiation thyroiditis manifested by anterior neck pain and dysphagia; two of the patients in the multiple dose group treated with three doses of 20 mc at weekly intervals were presented with similar symptoms. No additional cases of radiation thyroiditis have been observed with subsequent reduction in the weekly dose to 15 mc.

As of February, 1964, 21 of the 48 patients in this study are known to have died, the majority from arteriosclerotic heart disease.

**DISCUSSION**

The percentage of patients with induced hypothyroidism showing significant amelioration of angina in our series (76 per cent) is similar to the figures reported in previous studies (1-11). However, none of these studies includes mention of any patients showing worthwhile improvement in anginal symptoms de-

**Table I**

<table>
<thead>
<tr>
<th>Hypothyroidism Induced</th>
<th>Hypothyroidism Not Induced</th>
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<tr>
<td>Angina Improved</td>
<td>Angina Not Improved</td>
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<td>30 (76%)</td>
<td>9 (24%)</td>
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<td>6 (67%)</td>
<td>3 (33%)</td>
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<table>
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<th>Number of Patients and Percent</th>
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<td>30 months</td>
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<table>
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<tr>
<th>Average Duration of Follow-up</th>
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<tr>
<td>30 months</td>
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**Table I:** Efficacy of $^{131}I$ therapy in angina pectoris; the study group is divided into those patients in whom hypothyroidism was induced and those remaining euthyroid.
spite the persistence of euthyroidism. In the present study, six of the nine cases who remained euthyroid showed significant amelioration of anginal symptoms. While the significance of this finding in this relatively small number of patients is open to question, it points up clearly the difficulty in evaluating this or any other form of therapy in intractable angina pectoris.

The difficulties in the evaluation of drug therapy in the anginal syndrome might be predicted from the variable course of the underlying disease and the

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**SINGLE DOSE**

*Mean Dose* 23 mC ± 3.3 S.D.

16 Patients

- Hypothyroidism Induced
  - 14 Patients (87%)
    - Improved: 10 (71%)
    - Not Improved: 4 (29%)

- Hypothyroidism Not Induced
  - 2 (13%)
    - Improved: 1 (50%)
    - Not Improved: 1 (50%)

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**MULTIPLE DOSES**

*Mean Total Dose* 60 mC ± 24.4 S.D.

32 Patients

- Hypothyroidism Induced
  - 25 (78%)
    - Improved: 20 (80%)
    - Not Improved: 5 (20%)

- Hypothyroidism Not Induced
  - 7 (22%)
    - Improved: 5 (71%)
    - Not Improved: 2 (29%)

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Fig. 1. Comparison of results of ^131^I therapy administered as a single dose and in multiple doses.
markedly subjective nature of the patient's complaints. A double-blind study of so-called coronary vasodilators with multiple control periods (13) has shown that "none of the drugs used . . . consistently could be distinguished from its placebo by doctors or patients on the basis of its effect in decreasing chest pain". A more recent double-blind study (14) which evaluated the effectiveness of cobalt 60 teletherapy directed to the heart in severe angina showed that at 12 to 14 months following true or mock therapy (with shutter open or closed) no difference in response could be demonstrated between the irradiated and control groups with comparable "good results" in each. A double-blind study of the efficacy of thyroidal ablation with radioactive iodine is virtually impossible because of the characteristic signs and symptoms in hypothyroidism. Segal (8) has stressed the very real problem of patient evaluation following 131I therapy. He has employed a "lag period" of three weeks post therapy (during which no clinical improvement secondary to 131I therapy can be expected) to classify any patients who showed improvement in this period as "false responses" to therapy. Obviously, amelioration of angina despite the absence of any overt antithyroidal effect of 131I therapy as noted in our series limits the significance of the 76 per cent improvement rate in the group of patients rendered hypothyroid.

The 131I dosage schedules employed in the reported series have varied considerably. The original reports of Blumgart, et al (1-3) stress the use of single doses. Other groups have continued to use a similar dosage schedule (8, 9) or have modified Blumgart's approach by pre-treating the patients with propylthiouracil to increase the 131I uptake and diminish preformed hormone stores (10). In an attempt to reduce the incidence of radiation thyroiditis, Blumgart (7) administered doses of 10 mc to 20 mc weekly for three weeks. Jaffe (4, 6) has recommended smaller doses of 6 mc weekly for a period of five weeks. It would appear however, that whatever the dosage schedule employed, there has been no apparent difference in the overall efficacy of 131I therapy.

In our experience there was no significant difference in either the incidence of induced hypothyroidism or amelioration in angina whether the radioactive iodine was administered as a single dose (average 23 mc) or as three weekly doses (averaging 60 mc total dose). The initial motivation for the change from the single to multiple dose schedule lay in the attempt to obviate the occurrence of radiation thyroiditis. We have not observed any clinical evidence of radiation thyroiditis and there has been no apparent change in the incidence of post-131I hypothyroidism or the percentage of patients significantly improved with our present dosage schedule of three weekly doses of 15 mc each. It is of interest, however, that while only 12 percent of patients treated with the single dose method required an additional dose of 131I to induce hypothyroidism, 25 per cent of the patients treated with a multiple dose schedule remained euthyroid after the first course of therapy.

SUMMARY

The effectiveness of 131I ablative therapy in a series of 80 patients with intractable angina pectoris is evaluated. Meaningful follow-up information was available in 48 patients who constituted the actual study group. Thirty of 39
patients (76 per cent) rendered hypothyroid showed significant improvement. However, six of nine patients remaining euthyroid also showed significant improvement.

This study also affords a comparison of the single and multiple dose forms of $^{131}$I therapy and, aside from an apparent decrease in the incidence of radiation thyroiditis, no significant difference between these two forms of $^{131}$I therapy was noted. No attempt was made to compare the evolution of the anginal syndrome in a similar control group, and no allowance was made for the possible contributory role of other forms of medical therapy after the administration of radioactive iodine. No estimate of the effect of $^{131}$I therapy on survival was attempted.

Although the results achieved in this study are entirely comparable to those previously reported, the virtually identical improvement rate obtained in the smaller group of patients remaining euthyroid would seem to preclude meaningful assessment of the efficacy of this form of therapy.

REFERENCES


