Since hypothyroidism is commonplace after treatment of Graves' disease with radioiodine, the goal should be cure of hyperthyroidism rather than avoidance of hypothyroidism. To find the optimal dose to accomplish cure, we treated 605 patients with stepwise increasing doses of 3, 4, 5, 6, 8, and 10 mCi, analyzing the relationship of dose, age, sex, gland weight, and thyroidal uptake to cure. Estimates of cure at doses above 10 mCi were made from the literature. Cure was directly related to dose between 5 and 10 mCi. There was no significant relationship between cure and age (chi-square, p = 0.74), sex (chi-square, p = 0.12), and 24-hr uptake if over 30% (chi-square for slope, p > 0.10). Cure and gland weight had an inverse relationship (chi-square for slope, 0.01 < p < 0.02). We concluded that the optimal iodine-131 dose for curing hyperthyroidism is approximated by starting with 10 mCi and increasing it for unusually large glands or for special patient circumstances.

TABLE 1
Iodine-131 Dose (mCi) Versus Study Factors

<table>
<thead>
<tr>
<th>Study factors</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>8</th>
<th>10</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. patients</td>
<td>24</td>
<td>131</td>
<td>105</td>
<td>138</td>
<td>122</td>
<td>85</td>
</tr>
<tr>
<td>Age (yr, mean ± s.d.)</td>
<td>41.1</td>
<td>37.6</td>
<td>39.1</td>
<td>39.5</td>
<td>39.5</td>
<td>40.2</td>
</tr>
<tr>
<td>Sex (F:M)</td>
<td>13.0</td>
<td>12.2</td>
<td>10.9</td>
<td>13.5</td>
<td>14.1</td>
<td>11.9</td>
</tr>
<tr>
<td>Race</td>
<td>1.7</td>
<td>3.1</td>
<td>4.0</td>
<td>3.6</td>
<td>2.5</td>
<td>3.3</td>
</tr>
<tr>
<td>White (%)</td>
<td>12.5</td>
<td>17.6</td>
<td>16.2</td>
<td>18.1</td>
<td>20.5</td>
<td>16.5</td>
</tr>
<tr>
<td>Japanese (%)</td>
<td>41.7</td>
<td>39.7</td>
<td>39.1</td>
<td>34.1</td>
<td>35.3</td>
<td>22.4</td>
</tr>
<tr>
<td>Other (%)</td>
<td>45.8</td>
<td>42.8</td>
<td>44.8</td>
<td>47.8</td>
<td>44.3</td>
<td>61.2</td>
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<tr>
<td>Thyroid weight (g)</td>
<td>32.6</td>
<td>38.9</td>
<td>32.0</td>
<td>35.6</td>
<td>36.9</td>
<td>35.9</td>
</tr>
<tr>
<td>(mean ± s.d.)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>24-hr uptake (mean ± s.d.)</td>
<td>10.8</td>
<td>11.3</td>
<td>8.9</td>
<td>11.5</td>
<td>10.5</td>
<td>12.8</td>
</tr>
<tr>
<td>µCi/g (mean ± s.d.)</td>
<td>49</td>
<td>54</td>
<td>60</td>
<td>63</td>
<td>57</td>
<td>70</td>
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<td></td>
<td>16</td>
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<td>20</td>
<td>20</td>
<td>20</td>
<td>18</td>
</tr>
<tr>
<td></td>
<td>47.0</td>
<td>59.5</td>
<td>98.7</td>
<td>114.9</td>
<td>130.2</td>
<td>223.1</td>
</tr>
<tr>
<td></td>
<td>23.9</td>
<td>22.4</td>
<td>37.3</td>
<td>46.0</td>
<td>52.8</td>
<td>69.8</td>
</tr>
</tbody>
</table>

Thyroid Function Definitions

Hyperthyroidism was defined by the presence of clinical findings, elevated or high normal thyroid function tests, elevated or nonsuppressible thyroidal uptakes, and a flat response of TSH to TRH. Hyperthyroid patients were considered to have Graves' disease when the goiter (if present) was diffuse; ophthalmopathy and dermopathy provided additional verification. Euthyroidism was defined by the absence of signs or symptoms attributable to hyperthyroidism or hypothyroidism, a normal serum measure of thyroxine, and, since 1983, a normal TSH (IRMA). Hypothyroidism was defined by symptoms (if present), a low serum measure of thyroxine, and, since 1969, an elevated TSH.

Exclusions

Patients were excluded who had nodular hyperthyroidism by palpation or scan or euthyroid Graves' disease. In addition, six patients were excluded because they represented a small number in a treatment category—five treated with 7 mCi and one with 9 mCi.

Follow-up

Post-treatment follow-up examinations were done routinely at 6 wk without laboratory tests, at 3 mo and 1 yr with laboratory tests, and at other times as needed. Patients were classified as cured if the functional status was either euthyroid or hypothyroid at 1 yr without further treatment for hyperthyroidism during the year by drugs or radioiodine.

Iodine-131 Dosage

In 1960, a decision was made to give a fixed dose of 131I to all patients without regard to individual variables except under unusual circumstances, the most common being advanced cardiac disease. The fixed dose started with 3 mCi and it was increased to 4, 5, 6, 8, and 10 mCi. Pre-treatment with antithyroid drugs (ATDs) was done selectively, usually for patients who had severe hyperthyroidism, were debilitated, or had cardiac failure or arrhythmias. No patients had post-treatment ATDs.

Dose-Cure Curve

A curve was plotted to determine the proportion cured at each 131I dose level for all patients without regard to individual characteristics. Certain factors that have been reported to affect the cure rate (age, sex, goiter weight, and thyroidal uptake) were analyzed individually to determine their effect on cure. The proportion cured versus µCi/g of thyroid was calculated since that is a common approach in the literature (4,8,9,27-31).

Statistics

The chi-square statistic was used for discrete variables (sex, race) (32). Chi-square statistics for linearity and slope (33) were used to analyze the change in the proportion cured among grouped intervals of age, 131I dose, thyroid gland weight, 24-hr thyroidal uptake, and microcures of 131I per gram of thyroid weight.

RESULTS

Dose-Cure Relationship for All Patients Combined

Among 605 hyperthyroid patients treated with 3-10 mCi of 131I, 461 became euthyroid or hypothyroid, requiring no further treatment for hyperthyroidism—an overall cure of 76.2%. When patients were grouped by the amount of 131I administered, there was no increase in the proportion cured from 3 to 5 mCi (chi-square for slope, p > 0.10), but there was a progressive increase from 70% at 5 mCi to 87% at 10 mCi (chi-square for slope, 0.001 < p < 0.005). Cure between 5 and 10 mCi increased by 3.5% per added millicurie. Data from the literature for 356 patients treated with fixed doses of 15 or 16.2 mCi (Fig. 1) indicate a cure increase of 1.3% per added millicurie from 10 to 15.3 mCi (21,22,34).
FIGURE 1
Cure versus fixed dose. The solid line is the proportion cured (with 95% confidence intervals) for the patients we treated. The dashed line extrapolates the curve to the proportion cured based on the literature, a total of 356 patients (*) (see text).

Cure Versus Various Factors

Cures for "all patients combined were broken down by age, sex, race, thyroid weight, and 24-hr thyroidal uptake.

Age. Subdivided by decades of life, there was no significant tendency for the proportion cured to change with age (chi-square, p = 0.74).

Sex. Females had a slightly higher cure than males but it was not significant (chi-square, p = 0.12).

Race. Our patient population was 18% white, 35% Japanese, and 47% other races. The overall cure for whites was 86.9% (93/107), for Japanese 73.1% (155/212), for other races 74.5% (213/286). Differences among these groups were significant (chi-square, p = 0.015).

Thyroid Weight. Cure was inversely related to weight significantly (chi-square for slope, 0.01 < p < 0.02). Very large glands (over 60 g) had less cure and small glands (less than 30 g) had more cure, but cure for 65% of the glands between 30 and 60 g was not related to dose.

Thyroidal Uptake. Twenty-four-hour uptakes below 30% were associated with a lower cure. Between 30% and 100% of the glands, there was no relationship between uptake and cure (chi-square for slope, p > 0.10).

Cure Rate Versus \( \mu \text{Ci/g of Thyroid} \). For our data, there was a trend of increased cure with higher levels of \( \mu \text{Ci/g} \) (chi-square for slope, p < 0.001). Poor correlation was noted between cure rate and \( \mu \text{Ci/g} \) in data taken from the literature (Table 2).

DISCUSSION

The purpose of our study was to determine the relationship between the cure of hyperthyroidism and the amount of \(^{131}\text{I} \) administered. Clarifying this relationship makes it easier to choose a dose appropriate for the needs of each patient when cure of hyperthyroidism is the desired outcome.

Early investigators used complex formulas to estimate the dose that would cure hyperthyroidism with the least amount of hypothyroidism and the lowest dose of \(^{131}\text{I} \) (1,3). After it was found that hypothyroidism commonly occurred soon after doses sufficient to cure hyperthyroidism, attempts were made to reduce hypothyroidism by using small, often repeated, doses with early cure somewhat less important (2,31,35-39). More recently, it has been shown that hypothyroidism follows sooner or later in nearly all patients. Its occurrence within one or two years after treatment is related to dose (4,40), but delayed hypothyroidism develops at about the same rate regardless of the amount of \(^{131}\text{I} \) given (7,9,31,41,42). Elimination of hypothyroidism then becomes the central issue, and the pendulum is swinging towards larger doses, although most thyroidologists still support treatment to achieve the euthyroid state—100% in Japan (43), 80% in Europe (44), and 66% in America (45). The amount given for ablation has been arbitrary, usually around 15 mCi (21,22,34). This dose cures most patients but is unnecessarily high for the majority.

We have taken an intermediate position that provides a choice between the cure and persistence of hyperthyroidism but does not aim at ablation. Since cure varies directly with dose, it should be possible to estimate the cure rate at different amounts of \(^{131}\text{I} \) by using either a formula (e.g., \( \mu \text{Ci/g of thyroid} \)) or fixed millicurie doses. The outcomes from these alternative strategies are difficult to compare because of the broad range of millicurie doses given to individual patients when \( \mu \text{Ci/g} \) is held constant and the broad range of \( \mu \text{Ci/g} \) when the

<table>
<thead>
<tr>
<th>Authors</th>
<th>Reference Year</th>
<th>No. of pts</th>
<th>Mean ( \mu \text{Ci/g} )</th>
<th>% Cure</th>
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<tr>
<td>Smith RM et al.</td>
<td>36 1967</td>
<td>268</td>
<td>70</td>
<td>35</td>
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<td>Ross DS et al.</td>
<td>29 1963</td>
<td>61</td>
<td>75</td>
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<td>7 1974</td>
<td>102</td>
<td>80</td>
<td>74</td>
</tr>
<tr>
<td>Hagen GA et al.</td>
<td>2 1967</td>
<td>116</td>
<td>80</td>
<td>83</td>
</tr>
<tr>
<td>Ross DS et al.</td>
<td>29 1983</td>
<td>58</td>
<td>85</td>
<td>84</td>
</tr>
<tr>
<td>Moe RH et al.</td>
<td>52 1950</td>
<td>67</td>
<td>100</td>
<td>52</td>
</tr>
<tr>
<td>Bldda H et al.</td>
<td>47 1982</td>
<td>161</td>
<td>100</td>
<td>55</td>
</tr>
<tr>
<td>Kalk WJ et al.</td>
<td>18 1980</td>
<td>86</td>
<td>115</td>
<td>62</td>
</tr>
<tr>
<td>Smith RM et al.</td>
<td>36 1967</td>
<td>276</td>
<td>140</td>
<td>66</td>
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<td>Hagen GA et al.</td>
<td>2 1967</td>
<td>40</td>
<td>160</td>
<td>73</td>
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<tr>
<td>Cevallos JL et al.</td>
<td>7 1974</td>
<td>35</td>
<td>160</td>
<td>71</td>
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<tr>
<td>Seed L, Jaffe B.</td>
<td>10 1953</td>
<td>135</td>
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<td>Nofal et al.</td>
<td>53 1966</td>
<td>624</td>
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<tr>
<td>Scott GR et al.</td>
<td>54 1951</td>
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<tr>
<td>Kalk WJ et al.</td>
<td>18 1980</td>
<td>50</td>
<td>215</td>
<td>80</td>
</tr>
</tbody>
</table>

TABLE 2
Cure Rate Versus Single Dose of \(^{131}\text{I} \) Calculated as \( \mu \text{Ci/g of Thyroid} \) in Patients with Graves’ Disease
millicurie dose is held constant.

Using formulas that estimate μCi/g of thyroid, dose and cure correlate poorly in the literature (Table 2). This might be expected on the basis of thyroid weight alone, since it is so difficult to estimate weight by palpation even when it is done consistently by one person, as in our study, or aided by thyroid scintigraphy (3). However, the problem is more complex. Physical measurements are of questionable value in determining the appropriate dose because of variabilities in ultimate response to the radiation (12,13). We found no relationship between cure and uptake between 30% and 100%, and there was an inverse relationship between cure and thyroid weight but only at the extremes of large and small goiters. A calculation that combines these two elements to estimate dose is unlikely to be a good predictor of cure. Except for dose, gland sensitivity remains the strongest possibility for correlation with cure, but as yet there is no method to measure it.

The fixed dose approach is a simpler alternative for deciding on the amount of 131I to administer. We constructed a dose-cure curve as a guide to individualized treatment (Fig 1). At 5 mCi, the cure was 70% and at 10 mCi it was 87%.

To estimate the cure rate at fixed doses greater than 10 mCi it was necessary to review the literature since we had no data above that amount. The review was limited to studies in which Graves' disease patients were treated with fixed doses of 131I and were given no post-treatment ATDs, since that practice reduces radioiodine effectiveness (13,46,47). Three studies with a total of 356 patients had a weighted average dose of 15.3 mCi and a cure rate of 93.8% (21,22,34).

Our data combined with others suggest that the cure at fixed doses greater than 10 mCi is marginally better than the 87% cure at 10 mCi. Considering the common experience that some patients with Graves' disease require multiple doses, often in very large cumulative amounts (3,20,48-50), it is doubtful that all patients would be cured with one dose even at amounts greater than 15 mCi. Compared to the average gain of 3.4% per added mCi between 5 and 10 mCi, the gain for amounts above 10 mCi has little to offer when the goal is single-dose cure of hyperthyroidism with the smallest dose.

Concern for radiation has somewhat lessened (14-16). Gonadal radiation for the average dose is about equal to that of a barium enema and no increased risks of thyroid cancer, other malignancies, or genetic effects have been demonstrated. However, radiation risk is cumulative and effects may take generations to become apparent. It therefore seems prudent to keep radiation as low as feasible.

By observation of the dose-cure curve, it is possible to approximate the amount of 131I needed to match individual patient goals. For the large majority who have thyroidal uptakes over 30% and neither very large nor very small glands, 10 mCi appears to be the optimal dose. The choice of lower doses will reduce total-body radiation at the expense of more persisting hyperthyroidism; it will not decrease the rate of late hypothyroidism. The choice of higher doses may marginally increase the cure rate at the expense of increased radiation.

Cost is an additional consideration. If physician and patient agree upon 5 mCi because of concern about radiation or increased likelihood of hypothyroidism from the initial dose, it means accepting a 30% likelihood of additional treatment compared to 13% likelihood if 10 mCi is selected. The patient's direct cost in dollars, time from work, and morbidity increase markedly if the initial dose fails to cure.

This factor is sometimes entered into the equation when considering the amount of 131I to use (18,51), but it is brought more clearly into focus when the direct relationship between dose and cure is better appreciated. The option of 5 mCi incurs an average true cost considerably higher than 10 mCi if only the cost of office visits, laboratory testing, and the radioiodine treatment are considered, i.e., approximately double the cost when 30% of patients are retreated rather than 13% of patients. If extended disability and income loss are also considered, the average cost of an initial 5-mCi dose will be further increased compared to an initial 10 mCi dose.

For the reasons outlined, we believe that for most patients age, sex, uptake (if above 30%), and the avoidance of hypothyroidism should play minor roles in dose selection. Optimal 131I dose for curing hyperthyroidism is most simply attained by an initial dose of 10 mCi and increasing it for unusually large glands or for special patient circumstances.

ACKNOWLEDGMENTS

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REFERENCES

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Optimal 131I Dose in Graves' Disease • Nordyke and Gilbert
FIRST IMPRESSIONS

SUBJECT:
California Desert Tortoise (an endangered species)

PURPOSE:
We sought to evaluate the lower respiratory tract of a turtle. Radiographs of the subject were normal. Pulmonary perfusion study shows a uniform herringbone pattern and a craniocaudally-oriented photopenic strip due to attenuation by the shell and spine. The cranial view demonstrates a uniform uptake within the pulmonary parenchyma. Activity was present at the injection site and in the caudal vena cava, probably due to sluggish blood flow. Because the normal tortoise has a three-chamber heart (common ventricle), intracardiac shunting results in visualization of the kidneys. The study was considered normal.

TRACER:
0.8 mCi of 99mTc-MAA

ROUTE OF ADMINISTRATION:
Intravenous injection in the dorsal tail vein.

TIME AFTER INJECTION:
5 minutes

INSTRUMENTATION:
Raytheon Step-one/Step-two LFOV gamma camera interfaced with Technicare 560 imaging computer.

CONTRIBUTORS:
James J. Hoskinson, Gregory B. Daniel, and Richard S. Funk

INSTITUTION:
Departments of Urban Practice and Environmental Practice, College of Veterinary Medicine, University of Tennessee at Knoxville.