T₄ Suppression Test Involving 24-Hour Thyroidal ¹³¹I Uptake in Patients with Graves' Disease Compared to the T₃ Suppression Test

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Abstract

A T₄ suppression test involving 24-h thyroidal ¹³¹I uptake was carried out on patients with Graves' disease during therapy with an antithyroid drug. Thirty-three patients received propylthiouracil (PTU) for at least 1 year. Each patient was given 75 µg L-T₃ daily for 8 days in conjunction with PTU (50 mg/day) at the time of the experiment and then the 24-h thyroidal ¹³¹I uptake (post T₃ uptake was measured). Twenty-two patients had normal levels of serum T₃ and T₄-I before L-T₃ administration and were divided into 2 groups, positive T₃ suppression (post T₃ uptake ≤35%, group I) and negative T₃ suppression (post T₃ uptake >35%, group II). Eleven patients showed elevated serum T₃ or T₄-I concentrations before L-T₃ administration (group III). The T₄ suppression test was then performed on the same patients. Each patient was given 300 µg L-T₄ daily for 8 days in conjunction with PTU and the 24-h thyroidal ¹³¹I uptake (post T₄ uptake) was measured. Some patients receiving PTU (50 mg/day) were switched to MMI (5 mg/day) and the T₄ suppression test was done one month later. A significant correlation between the two suppression tests during PTU therapy was observed (r = 0.961, p < 0.01). None of the patients complained of side effects during the T₄ suppression test. The mean post T₄ uptake in group I was 18.8 ± 3.3% during PTU therapy and 5.4 ± 1.3% during MMI therapy. The mean post T₄ uptake in group III was 53.5 ± 7.0% during PTU therapy and 16.4 ± 5.8% during MMI therapy.

The present findings indicate that the T₄ suppression test with the lower toxicity reported herein is equivalent to the conventional T₃ suppression test. However, it appears to be difficult to evaluate the results of the T₄ suppression test on the basis of the 24-h uptake during MMI therapy.

The thyroid suppression test has been widely used to predict the outcome of medical treatment with antithyroid drug for Graves' disease (Werner and Spooner 1955; Cassidy 1965; Hales et al., 1969; Nagataki et al., 1974; Yamamoto et al., 1979). The classical method, originally designed by Werner and Spooner (1955), required the administration of 75 µg of T₃ daily for 8 days and then the measurement of 24-h thyroidal ¹³¹I uptake. However, some workers suggested that the T₃...
suppression test was accompanied by a severe adverse action on heart and circulation, due to the excess dose of T3 (Wallack et al., 1970; Mahlstedt and Joseph 1973; Wenzel and Meinhold 1974). Thus, the T4 suppression test was proposed using a single, 3 mg L-T4 dose without toxicity (Wallack et al., 1970; Mahlstedt and Joseph 1973; Wenzel and Meinhold 1974). This method was based on the concept that the average adult maintenance dose of L-T4 was 300 μg per day and the 3 mg L-T4 dose represented a 10 day supply (Wallack et al., 1970). However, many investigators revealed that the often recommended replacement dose of 300 μg L-T4 per day may be greater than that required to achieve the euthyroid states (Braverman et al., 1973; Maeda et al., 1976). We considered that a 300 μg dose of L-T4 daily might be useful in evaluating the thyroid suppressibility without toxicity, since a 300 μg dose of T4 was reported to be equivalent to a 75 μg dose of T3 (Werner 1978). On the other hand, the 24-h thyroidal radioiodine uptake was reported to be affected by antithyroid drug administration when compared to the very early uptake described previously (Thomas et al., 1960). However, Nagataki et al. (1974) revealed that there was little overlap between the suppressibility due to the 20-min uptake and the 24-h uptake even in patients receiving thionamide drugs. We have reported that there was a significant difference in the T₃ suppressibility due to the 24-h uptake between the antithyroid drugs employed (Kobayashi et al., 1983a). However, no detailed information was available regarding the effect of antithyroid drug on T₄ suppressibility due to the 24-h uptake.

The aim of the present study was to: 1) perform both the T₃ suppression test and the T₄ suppression test on the same patients and compare the suppressibility; 2) evaluate the T₄ suppressibility during the antithyroid drug therapy.

Materials and Methods

Thirty-three patients with Graves’ disease participated in the present study. All of the patients received 6-propyl-2-thiouracil (PTU) for periods of from 12 to 70 months. They were treated with a maintenance dose of PTU (50 mg/day) at the time of the study. Each patient was given 75 μg L-T₃ daily for 8 days in conjunction with PTU and then the 24-h thyroidal ¹³¹I uptake (post T₃ uptake) was measured. The positive T₃ suppression was defined as the 24-h uptake after T₃ administration lower than 35% (Werner and Spooner 1955; Nagataki et al., 1974; Kobayashi et al., 1983a). The twenty-two patients studied were regarded as euthyroid during antithyroid drug therapy, since their serum T₃ and T₄-iodine (T₄-I) concentrations were within normal limits and values for serum TSH were less than 10 μU/ml. They were divided into two groups, positive T₃ suppression (group I) and

<table>
<thead>
<tr>
<th>Group</th>
<th>n</th>
<th>Sex Ratio (female/male)</th>
<th>Age (y)</th>
<th>Therapy (Months)</th>
<th>Serum T₃ (ng/dl)</th>
<th>Serum T₄-I (μg/dl)</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>17</td>
<td>16/1</td>
<td>40±6#</td>
<td>28.1±5.0</td>
<td>142±7</td>
<td>5.0±0.3</td>
</tr>
<tr>
<td>II</td>
<td>5</td>
<td>3/2</td>
<td>42±8</td>
<td>20.5±4.1</td>
<td>151±4</td>
<td>5.6±0.6</td>
</tr>
<tr>
<td>III</td>
<td>11</td>
<td>10/1</td>
<td>39±5</td>
<td>19.8±2.0</td>
<td>386±7**</td>
<td>6.7±0.8</td>
</tr>
</tbody>
</table>

Studies were performed on 33 patients with Graves’ disease treated with PTU (50 mg/day). Twenty-two patients were regarded euthyroid, since their serum T₃ and T₄-I were within normal ranges. They were divided into 2 groups, according to the T₃ suppression test; the post T₃ uptake ≤35% (group I), the post T₃ uptake >35% (group II). Eleven patients had elevated serum concentrations of T₅ or T₄-I (group III). # Mean±SEM. ** p<0.01 vs. group I.
negative T3 suppression (group II). The eleven patients in group III had elevated serum T3 or T4-I levels (Table 1).

Two to four weeks after the T3 suppression test, the T4 suppression test was carried out on the same patients. Each patient was given 300 μg L-T4 daily for 8 days in conjunction with PTU (50 mg/day) and thyroidal 131I uptake (post T4 uptake) was measured. Some patients receiving PTU were switched to a maintenance dose of 1-methyl-2-mercaptoimidazole (MMI, 5 mg/day) and performed the T4 suppression test one month later.

Serum concentrations of T3, T4-I and TSH were determined as described previously (Kobayashi et al., 1980). Normal ranges for serum T3 and T4-I were 80–180 ng/dl and 3.0–7.0 μg/dl, respectively. The measurement of 24-h thyroidal 131I uptake was performed according to the method described by Nagataki et al. (1974). Statistical evaluation was made by Student’s t-test.

Results

Comparison of T3 suppressibility and T4 suppressibility

Both T3 suppression test and T4 suppression test were carried out on 33 patients. The results are shown in Fig. 1. There was a significant correlation between the results of the two suppression tests throughout the entire group of patients (r=0.961, p<0.01). Two of 17 patients in group I showed post T4 uptake values higher than 35%. In 5 patients from group II, none showed a post T4 uptake less than 35%. Eleven patients from group III had a post T4 uptake higher than 35%, although in 2 patients the post T3 uptake was less than 35%.

The mean post T4 uptake values for
Table 2. Comparison of the thyroidal ¹³¹I uptake and the incidence of side effects in T₃ suppression test and T₄ suppression test.

<table>
<thead>
<tr>
<th></th>
<th>Group I (n=17)</th>
<th>Group II (n=5)</th>
<th>Group III (n=11)</th>
</tr>
</thead>
<tbody>
<tr>
<td>24-h Thyroidal ¹³¹I Uptake</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(% of dose)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T₃ Suppression Test</td>
<td>15.6±2.0</td>
<td>55.2±6.4</td>
<td>60.7±5.4</td>
</tr>
<tr>
<td>T₄ Suppression Test</td>
<td>17.2±2.8</td>
<td>52.9±7.0</td>
<td>65.0±4.8</td>
</tr>
<tr>
<td>Side Effect</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(No. of Patients)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T₃ Suppression Test</td>
<td>4</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>T₄ Suppression Test</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

# Mean±SEM. There was no difference in the 24-h uptake values of the three groups between the T₃ suppression test and T₄ suppression test. T₃ suppression test showed side effects (palpitation or fatigability) in 8 of 33 patients studied. None of the patients complained of side effects during the T₄ suppression test.

these patients are summarized in Table 2. There was no significant difference in the 24-h uptake between the two suppression tests, regardless of the degree of suppressibility. None of the patients complained of side effects during the T₄ suppression test, while 8 of 33 patients (24.2%) became aware of fatigability or palpitation during the T₃ suppression test.

Changes in the serum T₃ and T₄-I levels after T₃ or T₄ administration

Fig. 2 shows the changes in the serum T₃ and T₄-I concentrations before and after L-T₃ or L-T₄ administration. During the T₃ suppression test, serum T₃ increased in all of the patients, although the increase in group III was not significant. On the other hand, serum T₄-I tended to decrease after T₃ administration, but this was not statistically significant in any group. In the T₄ suppression test, serum T₄-I was significantly increased by T₄ administration. Serum T₃ increased in group I and group II, although the increase in group II was not significant. In contrast, the serum T₃ concentration did not increase in group III.  

Comparison of T₄ suppressibility of various antithyroid drugs employed

The T₄ suppression test was repeated on the same patients receiving either PTU or MMI (Fig. 3). The post T₄ uptake values from group I during PTU treatment decreased remarkably in 12 of 14 patients after switching to MMI treatment. The mean post T₄ uptake was 18.8±3.3% during PTU therapy and 5.4±1.3% during MMI therapy, respectively (Table 3). Similar results were also obtained in group III. In four of 5 patients whose post T₄ uptake was more than 35% during PTU therapy, the values became less than 35% after switching to MMI therapy. The mean post T₄ uptake was 16.4±5.8% during MMI therapy and 53.5±7.0% during PTU therapy, respectively (Table 3).

Discussion

The present study indicated that our T₄ suppression test using daily dose of 300 µg L-T₄ for 8 days was equivalent to the conventional T₃ suppression test (Fig. 1, Table 2). Previous investigators recom-
Table 3. Comparison of serum T3, T4-I and post T4 uptake in PTU and MMI therapy.

<table>
<thead>
<tr>
<th>Group</th>
<th>PTU-treated</th>
<th>MMI-treated</th>
<th>n</th>
<th>Serum T3 (ng/dl)</th>
<th>Serum T4-I (μg/dl)</th>
<th>Post T4 Uptake (24-h, %)</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>14</td>
<td>14</td>
<td></td>
<td>140±6*</td>
<td>5.2±0.3</td>
<td>18.8±3.3</td>
</tr>
<tr>
<td>II</td>
<td>14</td>
<td></td>
<td></td>
<td>136±2</td>
<td>5.0±0.3</td>
<td>5.4±1.3***</td>
</tr>
<tr>
<td>III</td>
<td>5</td>
<td>5</td>
<td></td>
<td>300±5</td>
<td>7.0±0.4</td>
<td>53.5±7.0</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>280±9</td>
<td>7.0±0.5</td>
<td>16.4±5.8**</td>
</tr>
</tbody>
</table>

T4 suppression test was repeated on the same patients treated either with PTU (50 mg/day) or MMI (5 mg/day). Serum T3 and T4-I before L-T4 administration were shown. The post T4 uptake was significantly lower in the MMI therapy than in the PTU therapy. # Mean±SEM. ** p<0.01, ***p<0.001 vs. PTU-treated.
mended a suppression test with a single dose of 3mg L-T₄, which was reported to have lower toxicity (Wallack et al., 1970; Mahlstedt and Joseph 1973; Wenzel and Meinhold 1974). Mahlstedt and Joseph (1973) described how a suppression test measuring ⁹⁹ᵐTc uptake after a single dose of 3mg L-T₄ showed side effects in only 4% of the patients compared to 40% in the T₃ suppression test. In our T₄ suppression test, none of the patients complained of side effects, while 24.2% of the patients had uncomfortable sensations during the T₃ suppression test. Serum T₄-I concentrations after L-T₄ administration were significantly higher in the 3 groups than those that had pretreatment (Fig. 2). These observations are consistent with the concept that T₄ is probably a prohormone without metabolic activity, while T₃ is a biologically active hormone (Surks et al., 1973). In addition, mean serum T₃ concentrations after L-T₄ administration were less than 200ng/dl in group I and group II and the increase in group II was not significant. Although the exact reasons remain uncertain, it is possible that PTU treatment suppressed the peripheral conversion of T₄ to T₃ during L-T₄ administration (Braverman et al., 1971; Pittman et al., 1971). Thus, the T₄ suppression test presented herein appears to be a safer method for testing thyroid suppressibility than the T₃ suppression test. Similar criteria to those used for the T₃ suppression test could be
used for the T₄ suppression test (Fig. 1, Table 2).

We have demonstrated that in group I the post T₄ uptake was significantly lower in the MMI (5 mg/day) treatment than in the PTU (50 mg/day) treatment (Fig. 3). Even more interesting were group III patients who showed post T₄ uptake less than 35% in 4 of 5 patients after switching from PTU to MMI (Fig. 3). A similar result was also observed during the T₃ suppression test, indicating that the post T₃ uptake was significantly lower in the MMI-treated group than in the PTU-treated group (Kobayashi et al., 1983a). It is generally believed that the therapeutical potency of MMI is approximately ten times as great as that of PTU (Solomon 1971). The lower post T₄ uptake observed in the MMI therapy may be related to the greater inhibition of organic binding of iodide by MMI (Nagasaka and Hidaka 1976). The finding may be related to the qualitative difference in the action of the antithyroid drug employed, since PTU, but not MMI, was reported to inhibit the peripheral conversion of T₄ to T₃ (Braverman et al., 1971; Pittman et al., 1971). However, these possibilities are unlikely, since in both MMI and PTU therapy there was no difference in the serum T₃ and T₄-I levels before L-T₄ administration (Table 3).

We have reported that the serum T₄ level after L-T₃ administration was significantly lower in the positive T₃ suppression group than in the negative T₃ suppression group; the % of the initial T₄ value after L-T₃ administration was 68.4±2.5% in positive suppression compared to 91.2±6.5% in negative suppression (Kobayashi et al., 1983b). There was no difference between the decrease in serum T₄ after L-T₃ administration between MMI and PTU-treated patients, in either the positive T₃ suppression or negative T₃ suppression. The failure to show a significant decrease in the serum T₄-I after L-T₃ administration in the present study may be due to the insensitivity of the assay of serum T₄-I compared to the radio-immunoassay of serum T₄.

Whatever the mechanism of the lower post T₄ uptake in patients receiving MMI, the study may provide evidence that a daily dose of 5 mg MMI is more potent in lowering the post T₄ uptake than 50 mg PTU. It is of importance to note that some workers performed the test on the patients with antithyroid drug (Hales et al., 1969; Alexander et al., 1970; Nagataki et al., 1974), while others substituted thyroid hormone for the antithyroid drug at the end of the treatment (Cassidy et al., 1965). The results of the present study seem to indicate that the T₄ suppression test involving the 24-h uptake during MMI therapy is diagnostically misleading, as mentioned in connection with the T₃ suppression test (Kobayashi et al., 1983a).

References


