Thyrotropin Releasing Hormone (TRH) Stimulation Versus T3 Suppression in Assessing the Function of the Pituitary Thyroid Axis during Antithyroid Treatment in Hyperthyroidism

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The relation of the TRH test to the triiodothyronine (T3) suppression test was investigated in 43 patients with hyperthyroidism receiving antithyroid drugs for 6 to 27 months. All patients under study were in a euthyroid state, estimated by serum triiodothyronine uptake (T3U), thyroxine (T4), triiodothyronine (T3) and free thyroxine index (FT4I). The value for 24-hr. uptake after T3 administration was less than 20% in 18 cases, out of which the response to TRH was normal in 15 cases and was absent in 3 cases. On the other hand, out of 25 cases with a 24-hr. uptake value of more than 20%, the response to TRH was absent in 18 cases and was normal in 7 cases. The result of the TRH test correlated well with that from the T3 suppression test in 33 of 43 cases while in the other 10 cases the responsiveness of thyroid function to TRH was dissociated from its suppressibility with T3. This finding suggests that the TRH test cannot be a substitute for the T3 suppression test.

Key Words: Serum thyrotropin, Thyrotropin releasing hormone, 24-hour thyroidal 131I uptake, Thioamide drug, Euthyroid state, Criterion of cure of hyperthyroidism.

It is now widely recognized that patients with untreated hyperthyroidism are lacking in the response of serum thyrotropin to thyrotropin releasing hormone (TRH). Reported evidence indicates that restoration of a euthyroid state by treatment in such patients is associated, in most instances, with a normalization of the response to TRH but there are instances in which the responsiveness does not return even in the presence of euthyroidism.5

Those patients with hyperthyroidism who have been rendered euthyroid by antithyroid drug treatment and who demonstrate a suppression of thyroid function on the T3 suppression test have been reported to be less likely to relapse. Based on this fact, the T3 suppression test was regarded as providing a useful criterion of cure of hyperthyroidism.3 Recently, there has become available a T3 suppression test by 24-hour thyroidal 131I uptake which can be performed while the patient is on oral antithyroid drugs.6

In the study to be presented here the TRH and T3 suppression tests were performed on patients with hyperthyroidism who became euthyroid during antithyroid drug therapy in order to examine the re-

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relationship between therapy-induced recovery of TSH response to TRH and the suppression of thyroidal function by T₃.

PATIENTS AND METHODS

The subjects used in this study were 43 hyperthyroid patients, 39 females and 4 males, who ranged in age from 16 to 65 years. These patients were all in a euthyroid state after having received thioamide drugs (propylthiouracil or methimazole) for 6 to 27 months, the dosage of the drugs having been reduced to a minimum maintenance level of 50 mg or 5 mg daily. Judgment of euthyroidism in these patients was made on the basis of triiodothyronine uptake (T₃U), serum thyroxine (T₄) concentration, free thyroxine index (FTI) (estimated from the first 2 parameters) and serum T₃ concentration.

The TRH test was performed on the patients by administering 500 μg of TRH intravenously at 9 AM (while fasting) and determining the concentration of TSH in the serum from blood taken before and 15, 30, 45, 60, 90 and 120 minutes after TRH injection. Two weeks thereafter the T₃ suppression test was performed. The patients, while kept on oral antithyroid medication, were measured for 24-hour thyroidal I¹³¹ uptake after receiving 75 μg T₃ for 8 consecutive days and an oral I¹³¹ dose of 100 μCi on the following day. T₃U, serum T₄ concentration (displacement), serum TSH concentration (radioimmunoassay) and serum T₃ concentration (radioimmunoassay) were determined with the Triosorb kit, Res-O-Mat T₄ kit, HTSH kit and T-3 Riakit, respectively.

1. Triosorb kit and T-3 Riakit from Abbott Laboratories, Chicago, Ill.
2. Res-O-Mat T₄ and HTSH kit from Mallinckrodt Chemical Works, St. Louis, Miss.

RESULTS

Ten healthy subjects, 5 females and 5 males ranging in age from 20 to 40 years, gave serum TSH levels of 2.0 μU/ml to 6.0 μU/ml prior to the administration of TRH. Following a TRH dose the serum TSH was quickly elevated, reached a peak (10.1-31.4 μU/ml) in 15 to 45 minutes and then returned to the pre-TRH level at 120 minutes. Subjects showing a peak value of within or beyond this range were categorized as “responsive” while those whose peak values were below this range were classified as “unresponsive.”

The relationships between the duration of therapy, the post-T₃ 24-hour I¹³¹ uptake and the response to TRH administration for the entire 43 hyperthyroid patients are shown in Fig. 1. Of these 43, 22 responded to TRH (TRH test-positive) whereas the other 21 failed to respond to TRH (TRH test-negative). No particular relationship was noted between the presence or absence of response to TRH and the duration of antithyroid therapy.

The post-T₃ 24-hour thyroid I¹³¹ uptake was less than 20% in 18 cases and more than 20% in the remaining 25 cases. By categorizing cases showing a post-T₃ 24-hour thyroid uptake of less than 20% as “suppressible” and those showing an uptake value of greater than 20% as “nonsuppressible” and combining this classification with the TRH test results, the entire series of cases could be divided into the following 4 groups:

Group A: suppressible by T₃, TRH test-positive ......................15 cases
Group B: suppressible by T₃, TRH test-negative ..................3 cases

TRH Test and T₃ Suppression Test

Group C: nonsuppressible by T₃, TRH test-positive 7 cases
Group D: nonsuppressible by T₃, TRH test-negative 18 cases

Whereas in 33 of the 43 cases the results of the T₃ suppression test and of the TRH test were consistent with each other and a positive correlation was observed between the two tests, a dissociation was noted between the results of these tests in the remaining 10 cases. Table 1 gives the mean concentration of thyroid hormone in circulating blood at the time of these tests in each of the 4 groups defined above. As can be seen, there were no significant differences between any of the 4 groups in T₃U, T₄, FT₄ index and T₃.

Table 1. Thyroid function tests in patients with hyperthyroidism receiving antithyroid drugs grouped according to the suppressibility with T₃ and the responsiveness to TRH.

<table>
<thead>
<tr>
<th>Group</th>
<th>Suppression with T₃</th>
<th>Response to TRH</th>
<th>No. of patients</th>
<th>T₃U %</th>
<th>T₄ µg %</th>
<th>FT₄ index</th>
<th>T₁ ng/ml</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>+</td>
<td>+</td>
<td>15</td>
<td>27.3 ± 2.4*</td>
<td>7.7 ± 1.6</td>
<td>2.10 ± 0.40</td>
<td>1.12 ± 0.16</td>
</tr>
<tr>
<td>B</td>
<td>+</td>
<td>-</td>
<td>3</td>
<td>26.1 ± 0.1</td>
<td>7.6 ± 0.9</td>
<td>1.97 ± 0.22</td>
<td>0.97 ± 0.07</td>
</tr>
<tr>
<td>C</td>
<td>-</td>
<td>+</td>
<td>7</td>
<td>26.1 ± 3.0</td>
<td>7.3 ± 1.3</td>
<td>1.91 ± 0.43</td>
<td>1.32 ± 0.28</td>
</tr>
<tr>
<td>D</td>
<td>-</td>
<td>-</td>
<td>18</td>
<td>27.3 ± 4.1</td>
<td>8.7 ± 2.0</td>
<td>2.37 ± 0.64</td>
<td>1.36 ± 0.32</td>
</tr>
<tr>
<td>Control</td>
<td></td>
<td></td>
<td>29.9 ± 2.7</td>
<td>8.3 ± 1.7</td>
<td>2.44 ± 0.56</td>
<td>1.33 ± 0.27</td>
<td></td>
</tr>
</tbody>
</table>

* Mean ± S. D.

DISCUSSION

A reported study indicates that whereas in untreated hyperthyroidism high blood levels of thyroid hormone act on the pituitary gland to suppress the TRH-induced secretion of TSH, when return to a euthyroid state is brought about by antithyroid therapy there is a recovery of the response to TRH. However, there are cases in which restoration of euthyroidism is not followed by recovery of pituitary responsiveness to TRH. In fact, our present study indicates that approximately half of the cases failed to exhibit an appreciable response to TRH even after normalization of T₄, T₃ and FT₄ index was achieved. This finding is in keeping with a study which reported an absence of response to TRH with euthyroidism and normalization of T₃ following subtotal thyroidectomy in hyperthyroid patients. There is also a report stating that the administration of thyroid hormone results in suppression of the response to TRH even when it fails to cause T₄ and T₃ in the blood to rise beyond the normal range. However, as far as our present results are concerned, no significant difference was detected between cases with a response to TRH and those without it in both T₄ and T₃ levels. This suggests the possibility that some still unknown factor, besides the concentration of thyroid hormone in the circulating blood, might also be involved in the recovery of responsiveness to TRH.

The T₃ suppression test, as described originally by Werner, consists of 8-day oral dosage of 75 µg T₃ and measurement of 24-hour thyroidal ¹³¹I uptake prior to and after completion of this medication period. In healthy individuals this test yields a post-T₃ thyroid ¹³¹I uptake of less than 50% of the pre-T₃ uptake value and a post-T₃ 24-hour ¹³¹I uptake of less than 20% as a result of suppression of TSH secretion. Hyperthyroid patients give uptake values greater than those listed above. Using a method of measuring early thyroid uptake which reflects the iodide trap of the thyroid gland,
a parameter of thyroid function believed to be unaffected by antithyroid drug treatment, Alexander et al.\textsuperscript{3)\textsuperscript{)} carried out T\textsubscript{3} suppression tests and concluded that those patients whose post-T\textsubscript{3} 20-minute thyroidal \textsuperscript{131}I uptake is less than 50\% of the pretreatment 20-minute uptake or who give a post-T\textsubscript{3} 20-minute thyroid uptake value of less than 8\% are less likely to suffer a relapse after discontinuation of antithyroid medication. This method has since been used frequently as a means of evaluating prognosis after cessation of antithyroid drug therapy. The measurement of 24-hour thyroid \textsuperscript{131}I uptake during antithyroid drug treatment had been considered meaningless because of its vulnerability to the effect of antithyroid drugs. Contrary to this belief, Nagataki et al.\textsuperscript{4)\textsuperscript{)} performed T\textsubscript{3} suppression tests in patients while keeping them on an oral antithyroid drug regimen and found that 20-minute and 24-hour uptake values were in good agreement with each other. A T\textsubscript{3} suppression test which permits measurement of 24-hour \textsuperscript{131}I uptake without necessitating discontinuation of antithyroid medication has obvious advantages and this is the reason why this test was employed in our present study. In accordance with the original method of Werner a post-T\textsubscript{3} fall in 24-hour thyroid \textsuperscript{131}I uptake to less than 20\% was taken as the criterion for suppressibility of thyroid function.

In T\textsubscript{3} toxicosis the TRH test has been claimed to be of virtually the same diagnostic value as the T\textsubscript{3} suppression test.\textsuperscript{3)\textsuperscript{)} It has also been reported that in hyperthyroid patients on antithyroid drugs, elevated serum T\textsubscript{3} levels are associated with a lack of response to TRH and of suppression of thyroid function by T\textsubscript{3}. However, both tests return to normal with normalization of serum T\textsubscript{3} levels, which suggests that there is a good correlation between the two tests.\textsuperscript{9)\textsuperscript{)} Moreover, there have been reported cases of hyperthyroidism where euthyroidism and normality of serum T\textsubscript{3} level achieved by subtotal thyroidectomy were associated with an absence of response to TRH administration and nonsuppressibility of thyroid function by T\textsubscript{3}.\textsuperscript{6)\textsuperscript{)} It has thus become apparent that the two tests are consistent with each other and responsibility in both tests is not determined merely by serum levels of T\textsubscript{4} and T\textsubscript{3}, or free T\textsubscript{4} and free T\textsubscript{3}.\textsuperscript{10)\textsuperscript{)}

There are also reports of a dissociation of TRH and T\textsubscript{3} suppression test results. Franco et al.\textsuperscript{11)\textsuperscript{)} showed that among cases of euthyroid Graves' disease, those patients who were suppressible by T\textsubscript{3} administration responded to TRH administration, whereas only some of those patients who were non-suppressible by T\textsubscript{3} were responsive to TRH. Cases of ophthalmic Graves' disease who were responsive to TRH and unsuppressible by T\textsubscript{3} administration have also been reported.\textsuperscript{9)\textsuperscript{)}\textsuperscript{10)\textsuperscript{)} The fact that these cases had elevated LATS levels was thought to suggest the possibility that LATS might be involved in the nonsuppressibility of thyroid function by T\textsubscript{3}.\textsuperscript{9)\textsuperscript{)} However, evidences against this hypothesis has been published\textsuperscript{15)\textsuperscript{16)\textsuperscript{)} and the validity of this assumption is still debatable.

The purpose of our present study was to determine how and in what manner the TRH test is related to the T\textsubscript{3} suppression test, as the T\textsubscript{3} suppression test has been shown to be of value in the prognosis of relapse following cessation of antithyroid drug treatment in hyperthyroid patients. Out of our 43 cases, there was an association noted between the two tests in 33 cases, whereas in the other 10 cases a dissociation was observed. Of these 10 cases, 7 were nonsuppressible by T\textsubscript{3} administration but responsive to TRH. Such a dissociative phenomenon can be explained in the same way as that observed in euthyroid Graves' disease or ophthalmic Graves' disease. More particularly, it is due to the persistence of autonomy of the thyroid gland after return of TSH-secreting capacity to the pituitary gland under the influence of antithyroid drug therapy. In the remaining 3 cases, the suppressibility of thyroid function by T\textsubscript{3} was associated with a lack of response to TRH administration, a phenomenon which can not yet be explained.
by the current status of knowledge.

In summary, the present study has demonstrated that in patients with hyperthyroidism rendered euthyroid under the influence of antithyroid drug therapy, the TRH test usually correlates well with the T₃ suppression test, but some patients show a dissociation of the two tests. The results clearly indicate that the TRH test cannot be a substitute for the T₃ suppression test, there being a disparity in the underlying mechanism between the two tests.

REFERENCES