Effect of 3,5,3′L-Triiodothyronine Administration on Serum Thyroid Hormone Levels in Hypothyroid Patients Maintained on Constant Doses of Thyroxine

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Abstract

In order to investigate the effect of 3, 5, 3′L-triiodothyronine (T₃) administration on thyroid hormone concentrations in serum, thyroxine (T₄), T₃, 3, 3′, 5′L-triiodothyronine (reverse T₃, rT₃) and thyroid stimulating hormone (TSH) concentrations in serum were determined before and after T₃ administration in 10 hypothyroid patients maintained on constant doses of T₄.

Ten hypothyroid patients given 100 µg of T₄ for approximately 3 months had almost normal T₄ and T₃ concentrations in serum. Seven patients showed almost normal rT₃ concentrations in serum and they were slightly diminished in the remaining 3 patients. TSH levels in serum were almost within the normal limit in 7 out of 10 patients. However, despite the elevation of T₄ and T₃ levels, 3 patients had markedly elevated TSH levels.

Values for serum T₄ concentrations were decreased 4 weeks after the administration of 50 µg T₃ in all patients maintained on constant doses of T₄, although they were almost within the normal range. T₃ concentrations in serum, which was obtained just before the administration of the next daily doses of T₃, were markedly elevated in 6 of 10 patients after T₃ administration and the remaining 4 patients had also slightly higher T₃ concentrations than those before T₃ administration. On the other hand, serum rT₃ concentrations were diminished in 5 patients during T₃ ingestion. They were somewhat diminished or almost unchanged before and after T₃ administration in the remaining 5 patients. Moreover, 3 patients with elevated TSH levels during T₄ administration showed almost normal TSH levels after T₄ and T₃ ingestion.

The results showed the reciprocal relationship between T₃ and rT₃ levels in serum after T₃ administration in hypothyroid patients maintained on constant doses of T₄. Furthermore, the present findings suggest that the administration of both T₄ and T₃ might be a more suitable replacement therapy in the patients with hypothyroidism than T₄ alone.

It has been reported that the protein bound iodine (PBI) was decreased after 3, 5, 3′L-triiodothyronine (T₃) administration in hypothyroid patients maintained on the constant doses of thyroxine (T₄) (Farmer et al., 1969). However, the changes in serum T₃ and 3, 3′, 5′L-triiodothyronine (reverse T₃, rT₃) after T₃ administration have not been observed in detail.

In the present study, the effect of T₃ administration on serum T₄, T₃, rT₃ and thyroid stimulating hormone (TSH) concentrations was investigated in hypothyroid patients treated with constant doses of T₄.

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Materials and Methods

Clinical materials

Ten patients with primary hypothyroidism were given orally daily dose of 100 μg of T₄ for over 3 months in the outpatient clinic of Tenri Hospital. The daily replacement dose in micrograms of T₄ per kilogram body weight ranged from 1.54 to 2.5 μg/day/kg body weight (mean±SD=1.98±0.32 μg/day/kg body weight, Table 1). After they entered a clinically euthyroid state, 50 μg of T₃ was administered orally for about a month, while the dose of T₄ was kept constant. T₄ was given in 2 doses a day at 12 hr intervals and T₃ in a dose in the morning. The hormone preparations which were administered to these patients were L-T₃ (Thyronamine; Teikoku Zoki, Tokyo, Japan) and L-T₄ (Thyradin S; Takeda, Tokyo, Japan).

All the patients presented typical clinical pictures of hypothyroidism and they had a low basal metabolic rate (BMR) and T₄ concentrations with markedly elevated TSH levels before treatment. Patients with clinically detected liver or renal diseases were not included in this study.

Determinations of T₄, T₃, rT₃ and TSH concentrations in serum

Serum T₄ concentrations were determined according to the method of Murphy and Pattee (Murphy and Pattee, 1964), using the commercial kit provided by Mallinckrot/Nuclear, ST. Louis, USA. The normal range of T₄ was 4 to 13 ng/100 ml. Serum T₃ was measured by radioimmunoassay kit provided by the Dainabott Radioisotope Laboratories, Tokyo, Japan. Normal subjects had T₃ values ranging from 85 to 180 ng/100 ml. The determinations of rT₃ concentrations in serum were carried out with a radioimmunoassay kit purchased from Sereno Laboratories, Boston, USA. Serum rT₃ concentrations ranged from 22 to 39 ng/100 ml in normal volunteers. Serum TSH was measured with a radioimmunoassay kit provided by the Daiichi Radioisotope Laboratories, Tokyo, Japan. The normal limit of TSH values was under 5 μU/ml. There were no significant differences in T₄, T₃, rT₃ and TSH values for the same serum determined in two consecutive assays by the paired t test. Moreover, the coefficients of variation for triplicate determination within an assay in these hormones were under 7.2% in normal subjects.

The concentrations of T₄, T₃, rT₃, and TSH were determined in serum drawn before and 4 weeks after T₃ administration in hypothyroid patients maintained on constant doses of T₄. After treatment with T₄ and T₃, serum was obtained just before administration of the next daily dose in the morning. After separation by centrifugation, serum was stored at −20°C before use. In no case was there any evidence of a systemic change which would suggest alteration of the “steady state” during the course of the studies.

Results

Ten hypothyroid patients given 100 μg of T₄ for about 3 months had normal T₄ concentrations in serum (Table 1). Values for T₃ concentrations in serum ranged 80 to 148 ng/100 ml (mean±SD=122±22 ng/100 ml, Table 1) in these patients: values were almost within normal limits. Seven patients showed normal rT₃ concentrations in serum and 3 patients had low normal rT₃ concentrations (Table 1). After T₄ ingestion, TSH levels were less than 7.2 μU/ml in 7 patients and the remaining 3 patients still had markedly elevated TSH levels (Table 1). The daily replacement doses of T₄ per kilogram body weight in these 3 patients were 1.92 (T. N.), 1.61 (K. T.) and 2 (T. O.) μg/day/kg body weight, respectively (Table 1) and their T₄ and T₃ concentrations in serum were almost within normal limits.

Values for T₄ concentrations in serum were decreased 4 weeks after T₃ administration in all patients maintained on constant doses of T₄, although they were still within normal limits (Table 1). On the other hand, marked elevations in serum T₃ concentrations were found in 6 patients after T₃ administration, but 4 patients had slightly elevated T₃ concentrations, as compared with those before T₃ administration (Table 1). After T₃ administration, rT₃ concentrations in serum were diminished in 5 patients, although they were somewhat diminished or almost unchanged before and after T₃ administration in the remaining 5 patients (Table 1). rT₃ concentrations in serum averaged 21 ± 4 ng/100 ml after T₃ administration the value was significantly lower than that (mean±SD=25 ± 4 ng/100 ml) before T₃ administration by the paired t test (0.01 < p(|t|≥2.933) < 0.02, Table 1).
Table 1. Effect of T₃ administration on serum T₄, T₃, rT₃ and TSH concentrations in hypothyroid patients maintained on constant doses of T₄.

<table>
<thead>
<tr>
<th>No.</th>
<th>Subject</th>
<th>Sex</th>
<th>Age</th>
<th>Body weight (kg)</th>
<th>Daily dose of T₄ (µg/day/kg)</th>
<th>T₄ Before (ng/100 ml)</th>
<th>T₃ Before (ng/100 ml)</th>
<th>rT₃ Before (ng/100 ml)</th>
<th>TSH Before (µU/ml)</th>
<th>After (µU/ml)</th>
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<tbody>
<tr>
<td>1</td>
<td>T. N.</td>
<td>M</td>
<td>28</td>
<td>52</td>
<td>1.92</td>
<td>6.5</td>
<td>5.3</td>
<td>140</td>
<td>156</td>
<td>26</td>
</tr>
<tr>
<td>2</td>
<td>M. F.</td>
<td>F</td>
<td>30</td>
<td>40</td>
<td>2</td>
<td>5.7</td>
<td>4.2</td>
<td>95</td>
<td>145</td>
<td>19</td>
</tr>
<tr>
<td>3</td>
<td>Y. U.</td>
<td>F</td>
<td>31</td>
<td>40</td>
<td>2.5</td>
<td>5.5</td>
<td>5.1</td>
<td>137</td>
<td>148</td>
<td>26</td>
</tr>
<tr>
<td>4</td>
<td>K. M.</td>
<td>F</td>
<td>46</td>
<td>55</td>
<td>1.82</td>
<td>11.7</td>
<td>8.3</td>
<td>145</td>
<td>148</td>
<td>30</td>
</tr>
<tr>
<td>5</td>
<td>K. T.</td>
<td>F</td>
<td>47</td>
<td>62</td>
<td>1.61</td>
<td>7.1</td>
<td>5.7</td>
<td>80</td>
<td>140</td>
<td>23</td>
</tr>
<tr>
<td>6</td>
<td>H. M.</td>
<td>F</td>
<td>52</td>
<td>48</td>
<td>2.1</td>
<td>10.4</td>
<td>6.1</td>
<td>123</td>
<td>125</td>
<td>29</td>
</tr>
<tr>
<td>7</td>
<td>M. K.</td>
<td>F</td>
<td>54</td>
<td>65</td>
<td>1.54</td>
<td>7.4</td>
<td>5.1</td>
<td>100</td>
<td>304</td>
<td>22</td>
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<tr>
<td>8</td>
<td>T. O.</td>
<td>F</td>
<td>57</td>
<td>50</td>
<td>2</td>
<td>6.9</td>
<td>6.5</td>
<td>125</td>
<td>175</td>
<td>21</td>
</tr>
<tr>
<td>9</td>
<td>F. M.</td>
<td>M</td>
<td>67</td>
<td>55</td>
<td>1.82</td>
<td>9.0</td>
<td>5.5</td>
<td>148</td>
<td>248</td>
<td>27</td>
</tr>
<tr>
<td>10</td>
<td>T. K.</td>
<td>M</td>
<td>70</td>
<td>40</td>
<td>2.5</td>
<td>8.2</td>
<td>6.2</td>
<td>123</td>
<td>170</td>
<td>29</td>
</tr>
</tbody>
</table>

Mean ± SD:

<table>
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<th>p</th>
<th>Normal range</th>
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<tbody>
<tr>
<td>&lt;0.01</td>
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<tr>
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<td>85-180</td>
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<tr>
<td>&lt;0.02</td>
<td>22-39</td>
</tr>
<tr>
<td>&lt;5</td>
<td></td>
</tr>
</tbody>
</table>

Finally, the elevated TSH levels observed in 3 patients during T₄ administration were decreased almost to the normal range after both T₄ and T₃ administration (Table 1).

Discussion

In the present paper, serum T₄ concentrations were diminished after T₃ administration in hypothyroid patients maintained on constant doses of T₄, although they were still within the normal range. The results were consistent with those obtained by Farmer et al. (1969). On the other hand, serum T₃ concentrations were elevated after T₃ administration in patients maintained on constant doses of T₄. Previous studies (Surks et al., 1972; Saberi and Utiger, 1974) have shown that serum T₃ concentrations were increased transiently within the first 1–8 hrs after ingestion of both T₄ and T₃, and returned to the initial value about 24 hr after ingestion. In order to minimize the influence of ingested T₃ on serum T₃ concentrations, serum were obtained just before the administration of the next daily dose in the present study. A recent study (Chiraseveenuprapund et al., 1978), which investigated the conversion of T₄ to T₃ in rat kidney homogenate, has demonstrated that the addition of varying amounts of T₃ into the homogenate incubated with T₄ did not appreciably affect the rate of T₃ formation. They suggested that there was little inhibition of T₄ monodeiodination by the product T₃. Moreover, Grussendorf and Hübner (Grussendorf and Hübner, 1977) found that L-T₃ and D-T₃ very effectively increased the T₄ to T₃ converting activity of liver homogenate in thyroidectomized rat. Therefore, the elevation of the serum T₃ concentration after T₃ administration in the present paper might be partly due to an increase in T₃ production by the elevated conversion rate.

Recently, the determinations of rT₃ concentrations in serum by radioimmunoassay and the turnover studies of radioactive rT₃ have been made by several investigators (Chopra, 1974; Chopra, 1976; Burman et al., 1977; Gavin et al., 1977). They showed
that rT₃ as well as T₃ was a major product of T₄ monodeiodination and that a small proportion of rT₃ production arose directly from the thyroid. Thus, the majority of T₄ metabolized daily was monodeiodinated either to T₃ or to rT₃ and, therefore, the monodeiodination was an essential step in T₄ metabolism. It has been reported that the serum rT₃ concentration was increased in situations where serum T₃ was decreased (Chopra, 1974). These findings suggested that the 5'-'monodeiodination of T₄ was inhibited, resulting in the inhibition of T₃ formation and of rT₃ degradation (Kaplan and Utiger, 1978). In the present paper, serum rT₃ concentrations tended to diminish after T₃ administration in hypothyroid patients maintained on constant doses of T₄, while serum T₃ concentrations were elevated in these patients. The results suggest a reciprocal relationship between serum T₃ concentrations and rT₃ concentrations after T₃ administration in the patients maintained on constant doses of T₄. Thus, it seemed likely from the present findings that 5'-'monodeiodination of T₄ may be stimulated by T₃, causing an elevation in the rate of T₄ to T₃ conversion and of rT₃ degradation.

Since the previous study (Braverman et al., 1970) of athyreotic patients receiving L-T₄ therapy revealed normal or increased concentrations of serum T₃, because of the peripheral T₄ to T₃ conversion, it was well known that L-T₄ was a suitable agent in hormonal replacement therapy of patients with hypothyroidism (Stock et al., 1974; Braverman et al., 1973). In the present study, serum T₃ concentrations were elevated to the normal range after T₄ administration in hypothyroid patients. The results were consistent with those obtained by the previous study (Braverman et al., 1970). However, in the present study, it was noteworthy that 3 of 10 patients had still elevated TSH concentrations in serum, despite the administration of T₄ for approximately 3 months, although the doses were slightly less than the dosis (2.25 μg/kg body weight) recommended by the previous report (Stock et al., 1974). It has been suggested that adequate replacement therapy with L-T₄ would require doses sufficient to establish values for a serum T₄ concentration above the normal range (Sturnick and Lesses, 1961; Lavietes and Epstein, 1964). Moreover, the amount of T₃ generated by the conversion of T₄ to T₃ was found to contribute to approximately 70% of the daily T₃ production in normal subjects and, therefore, the 30% of the T₃ production was assumed to be secreted directly from the thyroid (Inada et al., 1975).

In the present paper, the elevated TSH levels found in 3 patients after T₄ administration were reduced to the normal range within 4 weeks after T₄ and T₃ administration. The present findings suggest that the administration of both T₄ and T₃ together might be more a suitable replacement therapy for patients with hypothyroidism than T₄ alone.

References


