Studies in hypothyroid rats show that, when infused with a combination of thyroxine (T4) plus triiodothyronine (T3) to normalize thyrotropin (TSH), euthyroidism in all organs is only ensured when T4 and T3 are administered in a ratio as normally secreted by the rat thyroid. As substitution with T4-only results in an abnormal serum T4/T3 ratio, it is also possible that in humans, euthyroidism does not exist at the tissue level in many organs, considering that iodothyronine metabolism in the human and the rat share many similar mechanisms. Recent reports in which cognitive function and well-being are compared in patients with primary hypothyroidism substituted with T4-only versus substitution with T4 plus T3 result in controversial findings in that either positive or no effects were found. In all these studies T3 was used in the plain form that results in non-physiologic serum T3 peaks. In these studies it is suggested that substitution with T3 should preferably be performed with a preparation that slowly releases T3 to avoid these peaks. In the study reported here we show that treatment of hypothyroid subjects with a combination of T4 plus slow-release T3 leads to a considerable improvement of serum T4 and T3 values, the T4/T3 ratio and serum TSH as compared to treatment with T4-only. Serum T3 administration with slow-release T3 did not show serum peaks, in contrast to plain T3.

Introduction

The introduction of synthetic levothyroxine for thyroid hormone replacement therapy several decades ago signified an important improvement over the use of desiccated thyroid powder that contained thyroxine (T4) plus triiodothyronine (T3) in a varying ratio because it was only standardized in its iodine content. Recent interest to return to a now stable T4/T3 combination that mimics normal serum thyroid function parameters as closely as possible, stimulated studies comparing the effects of substitution with T4 alone versus a fixed T4/T3 combination. These studies showed different results. Thus positive effects on health and well-being (1–3) as well as ineffectiveness (4–6) or even negative effects in some parameters (4) were noted. In two editorials (7,8) the pro and cons of these studies are discussed and suggestions were made for future studies to solve the discrepant findings. One of these recommendations is the use of T3 in sustained release manner. “Plain” T3 is rapidly absorbed into the bloodstream and also because of its short half-life of approximately 1 day, results in unwanted non-physiologic serum peaks (9). Already in 1993 in a review on the use and misuse of thyroid hormone it was stated: “Perhaps the truly ideal substitution therapy for hypothyroidism might be a combination of LT4, and LT3 in a carefully determined ratio and in a form in which the LT3 is slowly absorbed in a time-released form” (10).

In the present study we therefore addressed the following questions: (1) does a once-daily treatment with T4 and slow-release (SR) T3 lead to a constant serum T3 level without peaks and (2) does the use of a combination treatment of T4 plus SR-T3 in a specific ratio results in normalization of serum thyrotropin (TSH) T4, and T3 concentrations? To these ends, patients treated with levothyroxine (LT4) only for primary hypothyroidism were switched in an open, random, crossover manner to two regimens of substitution with a combination preparation of T4 plus SR-T3.

Materials and Methods

Patients

Inclusion criteria were: patients of either gender with primary hypothyroidism, using between 100 and 175 μg LT4 (Thyrox®, Organon BV, The Netherlands), preferably 150 μg, for at least 3 months. They should otherwise be healthy. Each patient gave written informed consent. Exclusion criteria were: the use of any other medication and age of 80 years and above.

Eighteen patients were selected, fulfilling the inclusion criteria. One patient was excluded because of vaso-vagal col-

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lapse after (the first) vena-puncture, 1 patient because of a car accident and subsequently hospitalization during the study, and 1 patient because of improper use of study medication. The 15 included patients consisted of 12 females and 3 males, with a mean age of 50 years (range 26–79 years). Fourteen patients were using 150 mg LT4 daily and 1 patient used 125 mg LT4 daily. The causes of primary hypothyroidism were: 131I treatment for Graves’ disease, Hashimoto’s thyroiditis, congenital hypothyroidism, neck irradiation for Hodgkin’s disease and subtotal thyroidectomy for nodular goiter.

Study design

Three 6-week periods were discerned. In the first 6 weeks the patients were kept on their LT4 dose that they were using before. Then patients were switched either to a combination therapy containing 125 µg T4 (Thyrax®, Organon BV) and 6 µg PL-T3 (inhouse normal release preparation using Cytomel® as T3 compound) daily, or to a combination therapy containing 125 µg T4 and 6 µg SR-T3 (in-house slow-release preparation and using Cytomel® as T3 compound). The combination treatments were performed in a randomized crossover design. During the sixth week of each study period, one blood sample was taken on day 3, and 5 serial blood samples were taken on day 5 at 8:00 AM (i.e., 15 minutes before ingestion of the medication), and at 09:45, 11:15, 2:15, and 5:15. Mean serum T4 and T3 and median serum TSH concentrations were calculated from the fifth day samples. It appeared that the T4, T3, and TSH values on the third day did not differ significantly from those on the fifth day at time point – 15 minutes, indicating that equilibrium was reached. Patients were at rest at least half an hour before each blood sample was taken.

Laboratory methods

Serum T4 and T3 were measured by in-house radioimmunoassay (RIA); TSH by Amerlite 30 Amersham, United Kingdom. Within-assay coefficients of variation were 2%–8% for T4, 2%–6% for T3, and 2–5% for TSH.

Calculations

Statistical analysis was either done with the paired two tailed test for T4, T3, T4/T3 ratios, the maximal concentration of T3 (Cmax), the time of the maximal concentration (tmax), and the area under the T3 curve from 0 to 24 hours (AUC0–24) or with the Mann-Whitney two-tailed test for TSH. The AUC0–24 was calculated by means of the linear trapezoidal rule, taking the predose value as the 24-hour point.

FIG. 1. Mean ± standard error of the mean (SEM) values of serum thyroxine (T4) (A), triiodothyronine (T3) (B), and T4/T3 (C) ratio and the median ± SEM of thyro-tropin (TSH) (D) during substitution with T4, T4 plus PL-T3 or T4 plus SR-T3 and in controls.
Results

The values of serum $T_4$, $T_3$, $T_4/T_3$ ratio, and TSH, during the different regimens, are depicted in Figure 1A–D. In Figure 1A, the mean value of $T_4$ during $T_4$-only substitution was not significantly different from the mean $T_4$ during $T_4 + PL-T_3$ ($p = 0.14$), but significantly higher during $T_4 + SR-T_3$ ($p = 0.025$) and in controls ($p < 0.0001$). The values of the combination treatments were not significantly different ($p = 0.67$). In Figure 1B, the mean serum $T_3$ during $T_4$-only treatment was significantly lower than during $T_4 + PL-T_3$ ($p = 0.0016$), $T_4 + SR-T_3$ ($p = 0.026$) and in controls ($p < 0.0001$). The mean serum $T_3$ during $T_4$ plus $PL-T_3$ was not significantly different from $T_4 + SR-T_3$ ($p = 0.23$). Figure 1C shows the mean $T_4/T_3$ ratio that was significantly higher on $T_4$-only than on $T_4 + PL-T_3$ ($p < 0.0001$), $T_4 + SR-T_3$ ($p < 0.0001$) and in controls ($p < 0.0001$), while the $T_4/T_3$ ratio on $T_4$ plus $PL-T_3$ was significantly lower than on $T_4$ plus $SR-T_3$ ($p = 0.026$). In Figure 1D, the median serum TSH on $T_4$-only treatment was not significantly lower than on $T_4 + PL-T_3$ ($p = 0.11$), but significantly lower than on $T_4 + SR-T_3$ ($p = 0.033$) and than in controls ($p < 0.0001$), while no significant difference was present between the two combination preparations ($p = 0.14$). TSH concentrations during treatment with $T_4 + PL-T_3$ and $T_4 + SRT_3$ were significantly lower than in controls (both $p < 0.0001$).

In Figure 2, the mean serum $T_4$ (Fig. 2A) and $T_3$ (Fig. 2B) and median TSH (Fig. 2C) are depicted for all subjects for each of the three regimens during the 9-hour sampling on the fifth day of the sixth treatment week. It can be seen that serum $T_4$ shows a limited but steady rise during sampling in all three treatments without any significant difference between them. During $T_4 + PL-T_3$, serum $T_3$ shows a considerable peak between 0 and 6 hours, whereas during $T_4 + SR-T_3$ no peak is present but a slight rise similar to $T_4$. No substantial change in $T_3$ concentrations is seen during $T_4$-only treatment. The pharmacokinetics of $T_3$ during both combination treatments are depicted in the Table 1. The data show that the AUC$_{0-24}$ of $T_3$ during both treatments are virtually

Table 1. Pharmacokinetic Parameters of Triiodothyronine (Mean ± SEM)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>$T_4 + PL-T_3$</th>
<th>$T_4 + SRT_3$</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>$C_{max}$ (nmol/L)</td>
<td>1.83 ± 0.06</td>
<td>1.67 ± 0.06</td>
<td>0.038</td>
</tr>
<tr>
<td>$T_{max}$ (h)</td>
<td>3.2 ± 0.56</td>
<td>4.97 ± 0.75</td>
<td>0.032</td>
</tr>
<tr>
<td>AUC$_{0-24}$ h (nmol.h/L)</td>
<td>37.97 ± 1.49</td>
<td>36.65 ± 1.43</td>
<td>0.43</td>
</tr>
</tbody>
</table>

$T_4$, thyroxine; PL-$T_3$, plain triiodothyronine; SR-$T_3$, slow-release triiodothyronine; $C_{max}$, maximal concentration; AUC$_{0-24}$, area under the curve from 0–24 hours; $T_{max}$, time point of $C_{max}$.
the same, while $C_{\text{max}}$ and $T_{\text{max}}$ of T3 during the SR-T3 regimen are significantly lower and later, respectively, than during PL-T3.

Discussion

Substitution of thyroid function with LT4 in patients with primary hypothyroidism, when titrated to normalize serum T4 results in a mean serum T3 level that is lower than normal. However, when T4 is administered in amounts to normalize serum T3, T4 parameters will rise to supranormal concentrations (11,12). The reason for this is that the thyroidal contribution to serum T3, which is approximately 20% of total serum T3 (13), is lacking in patients with absent thyroid function. Thus, in this situation all plasma T3 is derived from T4. Hence, in T4 substitution, more T4 has to reach the plasma compartment than under normal conditions to ensure normal plasma T3. Consequently, whatever dose of T4 is substituted, the serum T4/T3 ratio will always be abnormal, that is, elevated. It has been established in rats that the extent to which nuclear receptor-bound T3 is derived from plasma T3 and from local T3 production from T4 varies among tissues. Thus, for instance, nuclear T3 in cerebral cortex is derived for approximately 80% from local conversion of T4 in pituitary for approximately 50%, in skeletal muscle for approximately 40%, and in liver for only approximately 5% (14,15). When rats are infused with T4 in combination with T3 in the same ratio in which they are normally secreted, the euthyroid state in all of the many tissues studied is ensured. Any variation of this ratio leads to tissue hypothyroidism or hyperthyroidism in various organs (16).

Although the exact contribution of the different sources of nuclear T3 in human tissues is unknown, there are many similarities regarding thyroid hormone production and metabolism between rat and humans (17). Therefore, it would not be surprising if a similar situation with regard to the negative tissue effects of an abnormal plasma T4/T3 ratio would exist in humans as well. For instance, when T4 is administered in a dose such that serum T3 is normal, serum T4 parameters will be increased and serum TSH will be suppressed (18) because thyrotropic nuclear T3 occupancy is importantly dependent on plasma T4.

The ratio that we used in this study was based on data of thyroid hormone secretion and intestinal absorption in humans (19,20). The pharmacokinetics of T3 show that the slow-release preparation is indeed slowly releasing T3 in vivo as the $T_{\text{max}}$ occurs significantly later and the $C_{\text{max}}$ is significantly lower than in the case of plain T3. The total amount absorbed (see AUC) is the same for both preparations. Despite the fact that thyroid function parameters and the T4/T3 ratios improved substantially in the combination regimens, they were still not normal (Fig. 1). The combination treatment with slow-release T3 did not result in a serum T3 peak but only in a slow rise of T3 after intake, comparable to that of T4 (Fig. 2a and 2b). The relative variation of TSH in the three regimens is not different and one could wonder why during T4 plus PL-T3 serum TSH fluctuation is not at variance with that in the other two treatments. However, it should be realized that TSH secretion is importantly dependent on serum T4 (14,15), that may dilute any effect of serum T3 variations.

From this study it is apparent that using a slow-release T3 preparation, nonphysiologic T3 peaks are avoided. We suggest that in future studies on the effects of T4 plus T3, only sustained release T3 preparations are being used.

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