Treatment of Hypothyroidism with Once Weekly Thyroxine*

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ABSTRACT

We compared daily T₄ therapy with 7 times the normal daily dose administered once weekly in 12 hypothyroid subjects in a randomized cross-over trial. At the end of each treatment we measured serum free T₄ (FT₄), free T₃ (FT₃), rT₃, and TSH levels and multiple markers of thyroid hormone effects at the tissue level repeatedly for 24 h.

Compared with daily administration, the mean serum TSH before the administration of weekly T₄ was higher (weekly, 6.61; daily, 3.92 μIU/mL; P < 0.0001), and the mean FT₄ (weekly, 0.98; daily, 1.35 ng/dL; P < 0.01) and FT₃ (weekly, 208; daily, 246 pg/dL; P < 0.01) were lower. A minimally elevated serum total cholesterol during weekly administration (weekly, 248.8; daily, 292.8 mg/dL; P < 0.03) was the only evidence of hypothyroidism at the tissue level.

Compared with daily administration, the mean peak FT₄ following weekly administration of T₄ was significantly higher (weekly, 2.71; daily, 1.59 ng/dL; P < 0.0001), as was the mean peak FT₃ level (weekly, 285; daily, 246 pg/dL; P < 0.01). None of the tissue markers of thyroid hormone effect changed compared to daily T₄, and there was no evidence of treatment toxicity, including cardiac toxicity.

During weekly T₄ administration, autoregulatory mechanisms maintain near-euthyroidism. For complete biochemical euthyroidism a slightly larger dose than 7 times the normal daily dose may be required. (J Clin Endocrinol Metab 82: 870–875, 1997)

**T₄ REPLACEMENT for hypothyroidism usually achieves complete restoration of euthyroidism. However, daily, lifelong administration can lead to patient noncompliance. T₄ has an elimination half-life of about 7 days (1, 2), but its biological effect may be longer. It is a prohormone, the active hormone is T₃ (3, 4), formed from T₄ in peripheral tissues. There is strong evidence for autoregulation of the peripheral conversion of T₄ to T₃, with increasing conversion rates at low serum T₄ levels and decreasing conversion when serum T₄ is elevated (5–8). Together, these properties suggest the possibility of using a dosing interval longer than the traditional 24 h. Weekly dosing may improve compliance in some patients and could be advantageous to nurses or other caregivers when T₄ must be administered to patients unable to dose themselves.

During the 1960s through early 1980s, studies demonstrated that single doses of T₄ up to 3 mg are well tolerated (9–13). However, peripheral thyroid hormone measurements were largely limited to total serum T₄ and T₃ (11–13), although one study included radioactive iodide uptake, protein-bound iodine, T₃-resin uptake, and free T₄ (FT₄) in some patients (9). Sensitive TSH assays were not available, but two studies measured TRH-stimulated TSH responses (12, 13). No study measured free T₃ (FT₃). Although all studies commented to some degree on patient symptomatology, and one study measured total serum cholesterol (9), none assessed patient symptoms and thyroid hormone effects at the tissue level in a systematic or comprehensive fashion.

We, therefore, believed that the neither efficacy or safety of once weekly T₄ therapy was established and decided to determine this using current thyroid function tests and measurements of the tissue effects of thyroid hormone. The aim of the study was to determine whether 7 times the daily dose of T₄ administered once weekly was as safe and efficacious as the usual daily dose for maintenance therapy in hypothyroid subjects.

Experimental Subjects

The study protocol and all procedures were approved and monitored by the Capital Coast Health Ethics Committee (Wellington, New Zealand). All patients gave their informed consent.

Statistical power analysis

We used a randomized cross-over design for our study, thus achieving at least 4 times the statistical power of a comparably sized group comparative trial. We estimated that we needed 12 or more patients to achieve 80% power at the 0.05 significance level for detecting differences between daily and weekly treatment of 10–60% in the mean values of the tests performed. In addition, we ensured that the sample size was sufficient to detect a 10% difference in mean corrected systolic time intervals between the two treatments.
Patients

Fourteen patients were initially enrolled, and 12 subjects completed the study; 1 subject did not commence the study, and another patient developed chest pain of uncertain origin while receiving her normal daily T4 therapy and was withdrawn before entry into the weekly treatment phase. Two subjects were male, and 10 were female. The mean age of the study subjects was 50.8 (sd = 14.5) yr. All subjects suffered from confirmed primary hypothyroidism, as evidenced by a clearly elevated serum TSH at the time of diagnosis (≥20 mIU/mL) and at least 1 unsuccessful trial of T4 withdrawal thereafter. At the time of enrollment all had been receiving T4 replacement therapy at a stable dose for the least 3 months.

The mean daily T4 dose was 1.6 μg (sd = 0.35 μg)/kg BW. At the time of their original diagnoses, all patients had received standard instructions regarding T4 administration, including taking T4 separate from other medications and food.

The causes of hypothyroidism were autoimmune thyroiditis in five patients, radioiodine ablation in three patients, subtotal thyroidectomy in two patients, and undetermined in two patients. No patient suffered from severe medical illness, pituitary disease, untreated metabolic bone disease or osteoporosis, liver disease, cardiac disease, or known abnormalities of thyroid hormone metabolism and thyroid hormone protein binding or was taking medications known to interfere with thyroid function or thyroid hormone measurement.

Materials and Methods

Study design

At trial entry, subjects were randomly assigned either to continue with their usual daily maintenance dose of T4 or to take 7 times the usual daily dose once weekly, beginning on day 1 of the trial. Figure 1 summarizes the trial design. Three patients receiving other medications in addition to T4 continued to take these in the usual manner and dose during the duration of the trial, and all patients were instructed not to change their normal daily habits (including diet and exercise) during the trial period.

To achieve steady state serum thyroid hormone levels before testing,
all study subjects continued with their assigned T₄ treatment regimen for 6 weeks, about 6 times the elimination half-life of T₄. On the 43rd and 44th trial days, all subjects underwent clinical, biochemical, and biophysical tests. The patients taking a daily dose then took 6 times their normal daily dose on day 44 and omitted daily T₄ for the next 6 days. One week after testing (day 50) they then began taking 7 times their daily dose once each week for 5 weeks. Those subjects previously on the weekly dose returned to their daily dose 1 week after testing (day 50) and continued on the daily dose for the next 5 weeks. Testing was repeated on the 85th and 86th trial days.

On the days of testing patients attended the Department of Endocrinology, Wellington Hospital, between 0800–0900 h fasting. On arrival they underwent baseline testing (0 h), which comprised a standardized questionnaire concerning thyroid-related symptoms during the previous week, self-assessment of well-being during the previous week, self-assessment of well-being using a previously validated visual analog scale (14), and serum thyroid function tests, and measurement of a variety of serum analytes used as tissue markers of thyroid hormone effects. Depending on the treatment period, the subjects then took either their daily or weekly dose of T₄. Further blood samples were taken after 1, 2, 4, 8, and 24 h. Patients were permitted to eat after the 4-h testing. At 8 h, the echocardiogram was repeated. Patients receiving weekly treatment underwent an additional echocardiogram at 24 h (the 24 h echocardiogram was omitted in patients receiving daily treatment, because it was assumed to be equivalent to the baseline). The questionnaire and self-rated scale of well-being were readministered to all subjects at 24 h. All testing at 24 h was performed after an overnight fast and, for the patients receiving daily treatment, before T₄ was taken.

Details of the testing procedures are summarized in Fig. 1. Tables 1 and 2 provide an overview of the data. The leftmost edge (0 mm) corresponds to “worst ever.” The rightmost edge (100 mm) corresponds to “best ever.”

Serum assays

Thyroid function tests consisted of serum FT₄, FT₃, TSH (all measured on the Corning ACS-180+ automated immunoanalyzer, Scianz Corp., Auckland, New Zealand), rT₃ (measured by RIA, Biodata, Milan, Italy), and serum T₄-binding globulin [TBG; using an immunoradiometric assay (IRMA), Corning Medical, Midland, MI]. The functional sensitivity of the TSH assay is 0.03 mIU/mL. As general indicators of thyroid hormone effects at the tissue level, the following, previously validated, parameters (15–17) were used: sex-hormone-binding globulin (by IRMA, Orion Diagnostics, Finland); total cholesterol, high density lipoprotein (HDL), and triglycerides (Hitachi 717 multianalyzer, Boehringer Mannheim, Auckland, New Zealand); and apolipoprotein a (ApoA; immunoturbidimetric method, Hitachi 717). Low density lipoprotein (LDL) was calculated from HDL cholesterol and triglyceride concentrations.

To monitor the effects of thyroid hormone on the liver (17–21), aspartate aminotransferase, alanine aminotransferase, and γ-glutamyltransferase were measured with a Hitachi 717 multianalyzer.

Sodium osteocalcin and alkaline phosphatase were used as markers of the influence of thyroid hormones on bone turnover (22–24) and were measured with an IRMA (Nichols Institute, San Juan Capistrano, CA) and a Hitachi 717 multianalyzer, respectively.

Echocardiography

The cardiac effects of thyroid hormone were estimated by systolic time intervals (STI) measurements, a sensitive marker of these effects (15, 25–30). A two-dimensional echocardiogram was performed first, to exclude cardiac conditions known to interfere with STI measurements. The STI were obtained after the two-dimensional study and 15 min of rest by the method described by Tseng et al. (26), using a dual M-mode system (HP 7720AC Rev F, Hewlett-Packard, Palo Alto, CA) with a chart speed of 100 mm/s. Data were corrected for heart rate and gender (31), and a total of 10 cycles were analyzed to minimize variation due to respiration.

Data analysis

Data for TSH, FT₄, and rT₃ followed a log-normal distribution and were log transformed before analysis. Other noncategorical data did not need to be transformed before analysis. Statistical analysis of all data, except for the results of the symptom questionnaire, was performed using multivariate regression and ANOVA for repeated measures (32), with terms for treatment type (weekly vs. daily), treatment sequence (weekly or daily treatment first), and interactions. The Greenhouse-Geisser adjustment to degrees of freedom was used to account for the repeated measures on individuals (33). In addition, the untransformed TSH, FT₄, and rT₃ data were analyzed using nonparametric equivalents of the parametric statistical tests (Friedman test). The results of the symptom questionnaire were analyzed using McNemar’s test, comparing daily with weekly treatment (32). For all statistical tests, P < 0.05 was considered significant.

Results

Symptoms

All patients tolerated weekly T₄ treatment well. There were no significant differences at either 0 or 24 h between daily and weekly treatments in the results of the questionnaire and self-rated visual analog scale (Table 1).

Thyroid function tests

Serum thyroid hormone levels differed between weekly and daily treatment at several time points (Fig. 2). At 0 h, the mean values for FT₃ (daily, 424; weekly, 208 pg/dL; P < 0.01), rT₃ (daily, 26.75; weekly, 22 ng/dL; P < 0.01), and FT₄ (daily, 1.35; weekly, 0.98 ng/dL; P < 0.001) were significantly lower.

<table>
<thead>
<tr>
<th>TABLE 1. Results of the symptom questionnaire and visual analog scale of well-being</th>
<th>During the last week of treatment</th>
<th>During the 24 h after T₄ dose</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Daily T₄</td>
<td>Weekly T₄</td>
</tr>
<tr>
<td>Tired: Y/N; N</td>
<td>8/4</td>
<td>6/6</td>
</tr>
<tr>
<td>Nervous/anxious: Y/N; N</td>
<td>3/9</td>
<td>3/9</td>
</tr>
<tr>
<td>Constipated: Y/N; N</td>
<td>4/8</td>
<td>5/7</td>
</tr>
<tr>
<td>Loose bowels: Y/N; N</td>
<td>2/10</td>
<td>2/10</td>
</tr>
<tr>
<td>Cold: Y/N; N</td>
<td>5/7</td>
<td>2/10</td>
</tr>
<tr>
<td>Hot/sweaty: Y/N; N</td>
<td>2/10</td>
<td>2/10</td>
</tr>
<tr>
<td>Visual analog scale: mean distance from left edge (SD; mm)</td>
<td>63.5 (18.7)</td>
<td>57 (18.1)</td>
</tr>
</tbody>
</table>

a By McNemar’s test for paired proportions.

b The leftmost edge (0 mm) corresponds to “worst ever.” The rightmost edge (100 mm) corresponds to “best ever.”

c By Multivariate regression and ANOVA for repeated measures with Greenhouse-Geisser adjustment to degrees of freedom.

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for the group receiving weekly therapy. For this group, FT₄ was significantly higher at all other time points (all \( P < 0.005 \)), peaking at 2 h with both daily and weekly T₄ (daily, 1.6; weekly, 2.7 ng/dL). FT₃ was significantly higher with weekly than with daily T₄ at 4 h (daily, 240; weekly, 265 pg/dL; \( P < 0.04 \)) and 24 h (daily, 246; weekly, 285 pg/dL; \( P < 0.01 \)). FT₃ and rT₃ peaked later than FT₄. This delay was more pronounced with weekly T₄. Serum TSH levels with weekly therapy were significantly higher than with those with daily treatment at all time points (all \( P < 0.04 \)), except 24 h (\( P = \text{NS} \)). The largest difference occurred at 0 h, with a mean serum TSH value of 3.92 μIU/mL with daily T₄ vs. 6.61 μIU/mL with weekly T₄. Serum TSH levels with weekly T₄ fell rapidly in the first hour after T₄ administration and then gradually declined to levels similar to those with daily treatment.

Serum TBG results were subject to a treatment sequence effect, with measurements during weekly treatment significantly higher in patients who took daily T₄ first than in those receiving initial weekly treatment. We, therefore, only compared measurements during the first treatment cycle with either daily (\( n = 7 \)) or weekly (\( n = 5 \)) therapy. In this comparison the two treatment regimens did not differ significantly. Mean TBG values were between 1.99–2.04 mg/dL with daily and between 1.92–2.17 mg/dL with weekly treatment.

Markers of tissue effect

There were no significant differences at any time point between daily and weekly treatment in the levels of serum sex hormone-binding globulin, \( \gamma \)-glutamyltransferase, aspartate aminotransferase, alanine aminotransferase, osteocalcin, alkaline phosphatase (all in Table 2), HDL, and LDL (data not shown), but total serum cholesterol differed significantly at 0 h (\( P < 0.03 \)), with the mean being 14.2 mg/dL higher during weekly therapy (Table 2). No difference was found for serum total cholesterol measurements at other times. APOa was subject to a sequence effect. Consequently, as with serum TBG measurements, only the first treatment cycle was used for analysis. No differences between groups were found in serum APOa measurements.

STI measurements did not significantly differ between daily and weekly treatments (Table 2).

Discussion

Our results suggest that once weekly T₄ replacement therapy for hypothyroidism is safe and arguably efficacious, making it a possible alternative to customary daily therapy. Once weekly T₄ replacement was well tolerated, and there was no indication of acute treatment toxicity compared with daily therapy. Although serum FT₄ levels rose significantly after treatment, changes in FT₃ with once weekly therapy were slight, confirming previous studies (9, 11, 13). However, thyroid function tests demonstrated mildly hypothyroidism before weekly treatment, with higher mean serum TSH and lower mean serum FT₃ and FT₄ values. For complete biochemical euthyroidism, a slightly larger dose than 7 times the normal daily dose may be required.

At the peripheral tissue level, the effect of weekly T₄ treatment did not differ from that of customary daily treatment.
TABLE 2. Effects of once weekly T4 treatment on tissue markers of thyroid hormone effect

<table>
<thead>
<tr>
<th>Tissue markers of thyroid hormone effect</th>
<th>Mean (±SEM) at 0 h</th>
<th>Mean (±SEM) at 8 h</th>
<th>Mean (±SEM) at 24 h</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total cholesterol (mg/dL)</td>
<td>232.6 (12.3)</td>
<td>246.8 (13.6)</td>
<td>238.7 (12.8)</td>
</tr>
<tr>
<td>SHBG (nmol/L)</td>
<td>51.1 (11.2)</td>
<td>47.6 (8.4)</td>
<td>51.9 (12.6)</td>
</tr>
<tr>
<td>Liver</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AST (U/L)</td>
<td>10.4 (1.5)</td>
<td>9.3 (1)</td>
<td>11.3 (1.5)</td>
</tr>
<tr>
<td>ALT (U/L)</td>
<td>7.3 (1.4)</td>
<td>5.4 (1.3)</td>
<td>9.4 (1.9)</td>
</tr>
<tr>
<td>γGT (U/L)</td>
<td>32.8 (8.3)</td>
<td>30.6 (6.8)</td>
<td>30.1 (7.9)</td>
</tr>
<tr>
<td>Bone</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Osteocalcin (ng/mL)</td>
<td>4.6 (0.5)</td>
<td>3.9 (0.4)</td>
<td>4.8 (0.6)</td>
</tr>
<tr>
<td>Alkaline phosphatase (U/L)</td>
<td>51.5 (4.2)</td>
<td>51.9 (4.2)</td>
<td>53.9 (4.8)</td>
</tr>
<tr>
<td>Heart (STIs)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>69.1 (2.3)</td>
<td>66.6 (2.3)</td>
<td>69.8 (3.3)</td>
</tr>
<tr>
<td>R-R interval (s)</td>
<td>0.88 (0.03)</td>
<td>0.9 (0.04)</td>
<td>0.88 (0.04)</td>
</tr>
<tr>
<td>ICT (ms)</td>
<td>39.7 (2.7)</td>
<td>38.5 (2.4)</td>
<td>37.9 (1.7)</td>
</tr>
<tr>
<td>PEPc (ms)</td>
<td>108.7 (3.6)</td>
<td>108.9 (5.1)</td>
<td>109.3 (3.9)</td>
</tr>
<tr>
<td>LVETc (ms)</td>
<td>427.3 (10.6)</td>
<td>440.4 (11)</td>
<td>427.3 (9.5)</td>
</tr>
<tr>
<td>PEPc/LVETc</td>
<td>0.26 (0.01)</td>
<td>0.25 (0.01)</td>
<td>0.26 (0.01)</td>
</tr>
</tbody>
</table>

SHBG, Sex hormone-binding globulin; AST, aspartate aminotransferase; ALT, alanine aminotransferase; γGT, γ-glutamyltransferase; STIs, systolic time interval(s); ICT, isovolemic contraction time; PEPc, pre-ejection period corrected for gender and heart rate; LVETc, left ventricular ejection time corrected for gender and heart rate.

*Mean total serum cholesterol significantly higher (P < 0.03) on weekly T4. No statistically significant difference for any of the other measurements between daily and weekly T4.

**No statistically significant difference for any of the measurements between daily and weekly T4.

***For STIs, 24-h measurements of STIs were not performed for daily dosing.

****For STIs, at 24 h there was no statistically significant difference for any STI measurement with weekly T4 to corresponding 0 h values with daily T4.

despite differences in serum thyroid hormone levels. The only tissue marker of thyroid hormone effect to suggest hypothyroidism was total serum cholesterol at 0 h. This may have been due to statistical fluctuation. Furthermore, the observed rise was small and seemed to be caused by a rise in both HDL and LDL. It is generally believed that increased serum HDL levels may partially compensate for elevations in LDL (34). Hence, any potential adverse effect of the small rise in total serum cholesterol may have been mitigated.

One of the mechanisms maintaining near euthyroidism at the tissue level might be a change in the conversion rate of T4 to T3 (5, 6). Whereas serum FT4 levels almost tripled after the ingestion of weekly T4, FT3 rose by about 25%, and rT3 decreased by about 50%, suggesting preferential conversion of T4 to the metabolically inactive rT3. By contrast, at the end of the dosing interval, FT4 levels during weekly treatment were almost 30% lower than those during daily treatment, whereas FT3 levels were 15% lower, and rT3 levels were 18% lower. This indicates that at the end of weekly treatment, conversion of T4 to T3 increased, and conversion to rT3 decreased.

It could be argued that the tests of peripheral thyroid hormone effect employed were too insensitive and the number of subjects studied too small to detect subtle changes in the thyroid state. However, even in subclinical thyroid states most of the tests used are discriminatory (15–17, 20, 23–26, 35). STIs are shortened in patients with subclinical hyperthyroidism (25, 26) and lengthened in subclinical hypothyroidism (15, 26). All the changes observed are around 20% and within the range of the power of our study. The response of STIs to changes in serum thyroid hormone levels is rapid, showing significant differences in less than 2 weeks after the onset of hypothyroidism (28, 29).

However, continuous 24-h electrocardiogram monitoring, which generally parallels echocardiographic measurements of cardiac status (36), was not performed, and therefore, we cannot exclude the possibility of asymptomatic cardiac arrhythmia as a result of weekly T4 treatment. In addition, the absence of data on thyroid function tests and tissue markers during days 2–6 after weekly treatment in our study could underestimate the toxicity of weekly treatment. According to some studies, peak conversion of T4 to T3 may not occur until 2–4 days after the ingestion of large T4 doses (37, 38), although the rise after 24 h is slight if free T3 is measured (37). However, other studies have suggested that T4 doses between 2.4–300 mg will lead to a T3 peak before 24 h (11, 39). Our data suggest that FT3 levels plateau at around 4 h (and are in the lower third of the reference range), but we did not observe a fall in mean FT3 at 24 h. Consequently, we cannot completely dismiss the possibility of toxicity between days 2–6 after weekly treatment. However, in a pilot project involving two subjects (not included in this study) sampled at 0, 1, 2, 4, 8, 24, and 72 h, FT3 values at 72 h were between peak (24 h) and nadir (0 h) values.

As we do not have firm safety data for the period between 2 and 6 days after T4 administration or any direct assessment of potentially harmful arrhythmias, we would be hesitant to use weekly T4 treatment in individuals with ischemic heart disease who may be sensitive to T4 (18). We also do not know whether weekly T4 may be suitable to suppress TSH secretion, although our data suggest that the T4 dose will have to be increased significantly above 7 times the normal daily dose to ensure suppression over a week. An increase in the weekly dose above 7 times the patient’s usual daily dose might be possible without undue risk, but further study is needed on its effects on the skeletal system (22–24) and heart.
(36). Finally, in some patients weekly treatment could also be hazardous if several doses are missed. Clinicians and patient must work out a schedule that minimizes such risks before switching to weekly T4 therapy.

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References