Thyroid function tests during carbimazole therapy

D. L. SCOTT  
M.R.C.P.  

M. A. TAYLOR  
M.R.C.P.  

D. J. TYMMS  
M.R.C.P.  

C. CHAPMAN  
Ph.D.  

The Department of Nuclear Medicine, The General Infirmary, Leeds

Summary
Changes in plasma thyroxine (T₄), triiodothyronine (T₃), free thyroxine index (FTI) and thyroid stimulating hormone were studied in 100 patients with Graves' disease treated with carbimazole. During therapy plasma T₃ concentrations were disproportionately high compared to those of T₄, the T₄ : T₃ ratio was low, and many patients were clinically euthyroid with a normal plasma T₄ but low T₃ concentration. Although there was considerable individual variation in response, the order of response was always the same with plasma T₃ falling to normal or low levels before T₄. Plasma T₃ was the best indicator of clinical status and the best predictor of impending change; additional information of changes in thyroid status was obtained from plasma T₄ and FTI estimation, especially when these were followed sequentially. Single measurements of T₄ or FTI only are not recommended for assessing thyroid function during carbimazole therapy.

Patients and methods
One hundred patients with Graves' disease who were clinically thyrotoxic with raised plasma T₄ and T₃ concentrations before treatment were included. Those who had previous destructive therapy to the thyroid were excluded. All had at least 6 months' treatment with carbimazole, starting with doses of at least 40 mg daily and reduced to a maintenance dose of 5–20 mg daily. Eighteen were consecutive patients with Graves' disease who were studied prospectively from 1973–75 (group A). This group had a mean age of 47.2 years (range 11–67) and 16 were female. In the first months of therapy they were seen every 1–2 weeks and thereafter every 1–2 months. Their clinical status was assessed, and recorded as thyrotoxic (slight, moderate, or severe), euthyroid, or hypothyroid (slight, moderate, or severe). At each visit blood was taken for estimations of plasma T₄, T₃, thyroid stimulating hormone (TSH) and the thyroid hormone distribution index (THDI) from which the free thyroxine index (FTI) and the free triiodothyronine index (FTI) were calculated.

A further 82 consecutive patients with Graves' disease attending a thyroid clinic between 1976–78 were studied retrospectively (group B). These patients were seen at regular intervals, but less frequently than those in group A. They were assessed in a similar manner to the patients in group A and had similar laboratory tests with the exception of plasma TSH levels which were not measured routinely. The patients in group B had a mean age of 44.7 years (range 15–76) and 74 were females. Patients who were pregnant or taking the contraceptive pill were not included in either prospective or retrospective studies.

A control series consisted of 150 hospital outpatients who had thyroid function tests as part of
the routine assessment of conditions such as osteoporosis, diarrhoea, and alopecia. They were all clinically euthyroid, none was acutely ill or had been admitted as a medical or surgical emergency. They were selected sequentially, on an alphabetical basis, from patients attending in 1978 and had had estimations of plasma T₄, T₃, FT₄I and FT₃I. Their mean age was 44.9 years (range 14–67) and 131 were female.

Plasma T₃ and T₄ were measured by pre-precipitated double antibody radioimmunoassays, the distribution index as described by MacDonald, Chapman and Franklin (1976) and TSH by post-precipitated double antibody radioimmunoassay using material supplied by the National Pituitary Agency (U.S.A.); using as a standard the 1st International reference preparation human TSH 68/38.

Results

Before treatment, plasma T₄ and T₃ concentrations correlated exactly with the clinical assessment. During the first 6 months of treatment the clinical assessment in groups A and B agreed with the plasma T₃ on 64% of occasions, with the plasma T₄ on 54% of occasions and with both T₄ and T₃ on 39% of occasions. Detailed results are shown in Fig. 1.

The frequent assessment of group A patients provided detailed information of the changes initiated by carbimazole therapy (Table 1). The mean plasma T₄ concentration fell to normal by 2 weeks (individual variation 1–5 weeks); the mean FT₄I by 2 weeks (individual variation 1–4 weeks); the mean T₃ by 5 weeks (individual variations 1–26 weeks) and the mean FT₃I by 4 weeks (individual variations 2–26 weeks).

During treatment, T₄ entered the hypothyroid range in all the group A patients (varying in time from 5–22 weeks); T₃ entered this range in 12 patients. A transient rise in TSH was observed in 12 of the group A patients. These occasions were all preceded by a short period in which T₃ or FT₃I were in the hypothyroid range. Long periods during which T₄ and FT₄I were subnormal but T₃ and FT₃I were normal did not raise TSH above the normal range. Thyrotrophin releasing hormone (TRH) tests were not performed systematically. However, 3 group A patients had this test when their basal TSH was normal but all other biochemical parameters were below the normal range; in each case the 20-min TSH response to TRH was exaggerated. Clinical changes were even more variable and lagged behind

![Graph](http://pmj.bmj.com/)

**Fig. 1.** The relationship of plasma T₃ and T₄ to clinical status. The assessments were made during the first 6 months' carbimazole therapy in groups A and B. The results for plasma T₂ and T₄ are grouped as high, normal or low (reference ranges: T₃ 1.6–3.0 nmol/l; T₄ 60–140 nmol/l). The clinical assessment is given as thyrotoxic (■), euthyroid (□) or hypothyroid (■).

<table>
<thead>
<tr>
<th>Weeks of therapy</th>
<th>T₄ (nmol/l)</th>
<th>T₃ (nmol/l)</th>
<th>T₄ : T₃ ratio</th>
<th>FT₄I</th>
<th>FT₃I</th>
<th>TSH (i.u./l)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reference ranges</td>
<td>60–140</td>
<td>1.6–3.0</td>
<td>1.2–3.2</td>
<td>2.5–5.0</td>
<td>6–18</td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>218.8 (7.0)</td>
<td>7.35 (0.91)</td>
<td>33.8 (3.2)</td>
<td>6.15 (0.35)</td>
<td>22.10 (2.83)</td>
<td>8.7 (0.7)</td>
</tr>
<tr>
<td>1</td>
<td>166.9 (13.6)</td>
<td>5.51 (0.32)</td>
<td>30.4 (1.8)</td>
<td>3.84 (0.37)</td>
<td>12.3 (1.9)</td>
<td>8.8 (0.8)</td>
</tr>
<tr>
<td>2</td>
<td>122.6 (10.2)</td>
<td>4.03 (0.34)</td>
<td>29.0 (1.6)</td>
<td>2.54 (0.26)</td>
<td>8.22 (0.97)</td>
<td>7.3 (0.7)</td>
</tr>
<tr>
<td>3</td>
<td>106.2 (12.5)</td>
<td>3.87 (0.34)</td>
<td>26.6 (2.3)</td>
<td>2.00 (0.22)</td>
<td>6.64 (0.66)</td>
<td>9.9 (0.9)</td>
</tr>
<tr>
<td>4</td>
<td>95.3 (12.6)</td>
<td>3.17 (0.31)</td>
<td>30.1 (1.7)</td>
<td>1.48 (0.20)</td>
<td>4.89 (0.48)</td>
<td>9.6 (0.7)</td>
</tr>
<tr>
<td>5</td>
<td>84.4 (11.7)</td>
<td>2.88 (0.26)</td>
<td>26.6 (2.2)</td>
<td>1.15 (0.13)</td>
<td>3.92 (0.35)</td>
<td>9.3 (0.6)</td>
</tr>
<tr>
<td>6</td>
<td>77.9 (17.9)</td>
<td>2.77 (0.35)</td>
<td>23.4 (3.9)</td>
<td>0.84 (0.12)</td>
<td>3.24 (0.32)</td>
<td>12.8 (2.7)</td>
</tr>
<tr>
<td>7</td>
<td>54.9 (9.1)</td>
<td>2.19 (0.26)</td>
<td>24.0 (3.6)</td>
<td>0.86 (0.16)</td>
<td>3.34 (0.35)</td>
<td>12.4 (2.3)</td>
</tr>
<tr>
<td>8</td>
<td>44.1 (8.9)</td>
<td>2.09 (0.29)</td>
<td>22.5 (3.2)</td>
<td>0.61 (0.13)</td>
<td>2.63 (0.39)</td>
<td>16.7 (6.9)</td>
</tr>
<tr>
<td>9</td>
<td>44.9 (7.2)</td>
<td>1.82 (0.26)</td>
<td>22.3 (4.4)</td>
<td>0.72 (0.22)</td>
<td>2.83 (0.61)</td>
<td>19.8 (9.1)</td>
</tr>
<tr>
<td>10</td>
<td>39.6 (8.9)</td>
<td>2.37 (0.43)</td>
<td>18.3 (3.7)</td>
<td>0.62 (0.08)</td>
<td>3.05 (0.50)</td>
<td>20.4 (7.3)</td>
</tr>
<tr>
<td>11</td>
<td>56.7 (11.7)</td>
<td>2.39 (0.39)</td>
<td>23.7 (3.5)</td>
<td>0.65 (0.10)</td>
<td>3.10 (0.49)</td>
<td>18.0 (7.3)</td>
</tr>
</tbody>
</table>

**Table 1.** Carbimazole therapy: Initial changes in plasma T₄ and T₃ (±s.e. mean)
all the biochemical parameters measured in this study.

The considerable individual variation in response to carbimazole is illustrated by the detailed results of 2 patients (Fig. 2). Both patients were females given initial doses of 40 mg carbimazole daily. Patient W.S. had persisting 'T₃ toxicosis' during treatment, despite a fall in her plasma T₄ to hypothyroid concentrations. In contrast, patient D.S. had a rapid fall of both plasma T₄ and T₃ concentrations with a transitory rise in plasma TSH; her clinical status lagged behind the biochemical changes.

Five of the 100 patients had elevated plasma T₃ and FT₃I concentrations persisting for at least 6 months after commencing treatment. Clinically they were all mildly thyrotoxic, but their plasma T₄ and FT₄I concentrations had all rapidly fallen to normal or low levels. There was no evidence to suggest they were not taking carbimazole as prescribed and all responded to continuing high doses of carbimazole (30 mg or more daily). By one year they were all clinically and biochemically euthyroid.

The less frequent analysis of the 82 group B patients confirmed the findings seen in group A patients during carbimazole therapy. There was a rapid fall in T₄, followed by a slower and more variable fall in the concentration of T₃; clinical symptoms changed slower than both of these. The low T₄ : T₃ ratio seen in untreated Graves' disease was not 'normalized' by carbimazole therapy, and remained considerably below that of the hospital control group (Table 2).

**Discussion**

The disproportionately high plasma T₃ and low T₄ : T₃ ratio which is characteristic of untreated Graves' disease (Larsen, 1975), and occurs after radio-iodine and surgical treatment (Sterling et al., 1971), continues during carbimazole therapy. This is clearly shown by the results of this study and has been suggested from the results of a small survey by Linquette et al. (1978).

The response of the 18 patients in group A showed that during carbimazole therapy different parameters of thyroid function changed at different rates; the order of response was T₄, T₃, TSH and

![Graph showing plasma levels of T₄, T₃, and TSH over weeks of treatment for D.S. and W.S.]

**TABLE 2. Plasma T₄ and T₃ (± s.e. mean) in clinically euthyroid patients on carbimazole**

<table>
<thead>
<tr>
<th>Year of Carbimazole</th>
<th>T₄ (nmol/l)</th>
<th>T₃ (nmol/l)</th>
<th>T₄/T₃ ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reference ranges</td>
<td>60–140</td>
<td>1.6–3.0</td>
<td></td>
</tr>
<tr>
<td>Hospital controls</td>
<td>96.1 (1.9)</td>
<td>1.94 (0.03)</td>
<td>51.5 (1.2)</td>
</tr>
<tr>
<td>1–2 months' carbimazole</td>
<td>60.2 (4.8)*</td>
<td>1.87 (0.11)</td>
<td>32.6 (1.9)*</td>
</tr>
<tr>
<td>3–6 months' carbimazole</td>
<td>67.0 (3.3)*</td>
<td>2.06 (0.08)</td>
<td>34.3 (1.7)*</td>
</tr>
</tbody>
</table>

*Significantly different from hospital controls (P<0.001).
lastly clinical assessment. Similar observations were
made by Mortimer et al. (1977) in a study of 12
patients. There was marked individual variation
in response; in any individual patient, changes in
T₃, TSH, and clinical assessment could not be pre-
dicted from the T₄ values. In some patients, T₄ and
FT₄I were in the hypothyroid range and T₃ in the
hyperthyroid range. The divergence of T₃ and T₄
was most marked in the 5 patients with 'T₃ toxici-
sis' persisting for at least 6 months of treatment. This
has previously been reported in a single case by
Hollander et al. (1972) and in a small survey by
Bellabarba and Tremblay (1972).

Plasma T₃ was the best indicator of thyroid status
and the best predictor, in sequential series of results,
of impending changes in clinical status. This con-
clusion is in keeping with the work of Shenkman,
Mitsuma and Hollander (1973), who showed that
TSH responsiveness correlated best with T₃ concen-
trations during acute propylthiouracil therapy.
Similarly Hamada et al. (1978) have shown that
during long-term treatment with anti-thyroid drugs
the basal metabolic rate correlates best with plasma
T₃.

Plasma T₃ estimations give the most clinically
useful information to the physician during carbi-
mazole therapy. Plasma T₄ and FT₄I estimations
give further information of changing thyroidal function
and in conjunction with plasma T₃ estimations this
may be clinically valuable. Serial estimations give
the most useful information, especially when all
parameters are measured; it is the authors' policy
routinely to monitor these 3 indices during carbimazo-
le therapy. Many clinicians and laboratory
workers have been influenced by the work of Britton
et al. (1975) who suggest the free thyroxine index is
the measurement of choice to assess thyroid func-
tion. This is clearly not the case during carbimazole
therapy and is unlikely to be true for diagnosing
thyrotoxicosis since it is not always elevated in this
situation. Although the costs of laboratory tests are
important, the decision not routinely to measure T₃
concentrations restricts valuable clinical information,
and may not actually save money (Chapman and
Hayter, 1978). It is suggested that laboratories not
routinely measuring T₃ should reconsider their
policy. The dose schedule for carbimazole used in
this series is one that is generally recommended for
treating Graves' disease, although the variation
between individuals in response to carbimazole
shows that no single therapeutic regimen is appro-
priate for all patients.

Acknowledgment
We thank Dr C. J. Hayter for his help with this study.

References
Bellabarba, D. & Tremblay, R. (1972) Serum patterns of
thyroxine and triiodothyronine after the treatment of
thyrotoxicosis with anti-thyroid drugs. International
Journal of Clinical Pharmacology, 6, 18.

Britton, K. E., Quinn, V., Braun, B. L. & Ekins, R. P.
(1975) A strategy for thyroid function tests. British Medical
Journal, 3, 350.

diagnostic tests. British Medical Journal, 2, 830.

De Groot, L. J. & Stanbury, J. B. (1975) The Thyroid and
its Diseases, 4th Edn, p. 342. John Wiley & Sons, New
York.

Hamada, N., Miuwa, T., Ban, Y., Momotani, N., Nishik-
wana, Y., Ohno, M., Mori, H., Kitabatake, S. & Ito, K.
(1978) Closer correlation between serum triiodothyro-
line and basal metabolic rate during antithyroid treatment in
patients with Graves' disease. Endocrinologia japonica,
25, 117.

Hoffenberg, R. (1973) Triiodothyronine, Clinical Endo-
crinology, 2, 75.

Hollander, C. S., Shenkman, L., Mitsuma, T. & Asper,
S. P. (1972) Triiodothyronine toxicosis developing during
antithyroid drug therapy for hyperthyroidism. Johns
Hopkins Medical Journal, 6, 184.

Larsen, P. R. (1975) Thyroid triiodothyronine and thyro-
xine in Graves' disease: correlation with presurgical
thyroid status, and iodine content. Journal of Clinical
Endocrinology and Metabolism, 41, 1098.

Linquette, M., Lefebvre, J., Benoit, G. & Racadot, A.
(1978) Les hormones thyroïdiennes plasmatiques au cours
du traitement des hyperthyroidies par le carbimazole.
Annals d'Endocrinologie, 39, 83.

Thyroid-pituitary response to cardiopulmonary by-pass.
British Journal of Anaesthesia, 48, 225.

Mortimer, C. H., Anderson, D. C., Liendo-Ch, P.,
Thyrotoxicosis: relations between clinical state and bio-
chemical changes during carbimazole treatment. British
Medical Journal, 1, 138.

Nicoloff, J. T., Low, J. C., Dussault, J. H. & Fisher, D. A.
(1972) Simultaneous measurement of thyroxine and triiodo-
thyronine peripheral turnover kinetics in man. Journal of
Clinical Investigation, 51, 473.


Shenkman, L., Mitsuma T. & Hollander, C. S. (1973)
Modulations of pituitary responsiveness to thyrotrophin
releasing hormone by triiodothyronine. Journal of Clinical
Investigation, 52, 205.

York.

Sterling, K., Brenner, M. A., Newman, E. S., Odel, W. D.
& Bellabarba, D. (1971) The significance of triiodo-
thyronine in the maintenance of euthyroid status after
the treatment of hyperthyroidism. Journal of Clinical Endo-
ocrinology, 33, 729.

Utiger, R. D. (1974) Serum triiodothyronine in man,
Annual Review of Medicine, 25, 289.
Thyroid function tests during carbimazole therapy.

D. L. Scott, D. J. Tymms, M. A. Taylor and C. Chapman

Postgrad Med J 1980 56: 838-841
doi: 10.1136/pgmj.56.662.838

Updated information and services can be found at:
http://pmj.bmj.com/content/56/662/838

Email alerting service

These include:
Receive free email alerts when new articles cite this article. Sign up in the box at the top right corner of the online article.

Notes

To request permissions go to:
http://group.bmj.com/group/rights-licensing/permissions

To order reprints go to:
http://journals.bmj.com/cgi/reprintform

To subscribe to BMJ go to:
http://group.bmj.com/subscribe/