Medical therapy of Graves’ disease: effect on remission rates of methimazole alone and in combination with triiodothyronine

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Abstract
In a prospective, randomized study of 135 newly diagnosed patients with hyperthyroidism due to Graves’ disease we compared the effect on remission rates of additional triiodothyronine (T3) with conventional antithyroid drug therapy. To this end 114 patients were followed for at least 12 months (15.7 ± 4.9, mean ± s.d.) after the discontinuation of any therapy. After return of thyroid function to normal (8.5 ± 7.4 weeks, mean ± s.d.) patients were maintained on antithyroid medication for 9.0 ± 2.5 months. They were then randomly assigned to one of three groups: group 1 (n = 44) stopped methimazole, groups 2 (n = 39) and 3 (n = 31) continued with exogenous T3 (not exceeding 75 mg/day in any patient) for a further 6 months either with (group 2) or without (group 3) a fixed dose of 10 mg methimazole daily. The T3 dose was kept variable to keep TSH suppressed (< 0.1 mU/l), which could be achieved in 82% of patients on 100% of their monthly visits. No serious side-effect requiring the discontinuation of the study occurred in any patient. Total T3, TSH-receptor antibodies and some previously suggested potential predictors of relapse including thyroid size by ultrasound, 24 h urinary iodine excretion, history of cigarette smoking and ophthalmopathy were determined at the outset of the study and subsequently every 6 months (and total T3 every 4 weeks).

No significant difference (P > 0.05, Chi square) was seen in relapse of hyperthyroidism after a mean follow-up of 16 months (range: 12–31 months; groups 1: 52%, 2: 44% and 3: 42%) in an area of low-to-moderate iodine intake (prevalence of 24 h urinary iodine excretion < 100 mg/24 h: 17 and 25% at two different measurements respectively). Concomitantly, no predictor of recurrence of disease could be identified, irrespective of treatment modality.

European Journal of Endocrinology 142 117–124

Introduction
Graves’ disease is a common autoimmune disorder with a prevalence of 2% in females and 0.2% in males (1). Radioiodine ablation of the thyroid gland, surgery (near total or total thyroidectomy) and medical therapy with antithyroid drugs are the three options available for treatment. While in the USA radioiodine therapy is most often chosen as initial therapy, European and Japanese centers prefer antithyroid drugs when referring to the same ‘index’ patient (2). Recently, increases in mortality from all causes and mortality due to cardiovascular and cerebrovascular disease and fractures among patients with hyperthyroidism treated with radioiodine (3) and the putative negative influence of radioiodine on preexisting ophthalmopathy (4) may have triggered renewed interest in medical therapy.

Patients treated with thyrostatic drugs have a roughly 40% chance of long-term remission (5). Putting the thyroid at rest by suppression of thyrotropin (TSH) with exogenous thyroxine (T4) in addition to thyrostatic medication alone was initially thought to be beneficial (6) and improved remission rates were found in two studies (6, 7). This finding was related to alteration of the ongoing intrathyroidal immune reaction, possibly by a diminished antigen presentation (8). In addition, beneficial effects of triiodothyronine (T3) added to thyrostatic therapy could be based, besides continued suppression of TSH, on negative feedback by thyroid hormone on thyroid nuclear receptors (9). Some more recent studies have, however, not shown any difference in response to added thyroid hormone on either remission rates or TSH-receptor antibody (TRAb) concentrations (10–15).

Because of these conflicting results we have conducted a prospective, randomized study in patients with newly diagnosed Graves’ disease in an area of high goiter prevalence and compared the outcome of treatment with methimazole alone with that of the combination of methimazole plus T3. Since frequency of relapse has been related to iodine intake in patients...
treated with methimazole alone (16–18), urinary iodine excretion was determined.

Materials and methods

Subjects

One hundred and thirty-five patients (mean age: 41 years; range: 15–74), with newly diagnosed, previously untreated Graves’ disease entered the study. Exclusion and drop-out criteria were as follows: cardiovascular, renal, pulmonary, gastrointestinal, endocrine, psychiatric or neoplastic disease, plain T3-hyperthyroidism, impending thyrotoxicosis, relapse of Graves’ disease, multinodular goiter and pregnancy. Twenty-one patients dropped out due to their inability to comply with study requirements (n = 10), because they moved away (n = 8) or because of pregnancy (n = 3). No serious drug reactions occurred. One hundred and fourteen patients (n = 113 Caucasians, n = 1 African) were followed for at least 12 months (mean 6 S.D. 15.7 ± 4.9) after the discontinuation of any therapy and are the basis of this report. Diagnosis of Graves’ disease was by clinical symptoms and biochemical evidence of hyperthyroidism (Table 1) and a rapid and diffuse thyroidal uptake of technetium. All patients had 99mTc scintigrams and determinations of TRAb concentrations (Table 1) at the start of the study. By ultrasound 17 of 114 (15%) patients had thyroid nodules which upon fine needle aspiration were benign (n = 14) or had follicular neoplasia (n = 3, which were benign upon surgery) and were included in the study because of additional indirect evidence of Graves’ disease (ophthalmopathy: n = 10, slightly elevated TRAb concentrations in young patients: n = 7). Young age, however, has not been considered a criterion by itself for the diagnosis of Graves’ disease.

Study design

Initially all patients were treated with 60 mg methimazole daily for 1 week followed by 40 mg per day for 1 week and 20 mg daily for week 3. After 3 weeks thyroid function was controlled to adjust the antithyroid medication. Thereafter, patients were seen at intervals of 4–6 weeks throughout the study. The time necessary to have serum total T3 (TT3) and serum total T4 (TT4) concentrations within the normal range (TT4: 5.0–11.2 μg/dl and TT3: 0.8–1.9 ng/ml) was 8.5 ± 7.4 weeks (mean ± S.D.). All patients then were maintained on methimazole alone for a total of 9.0 ± 2.5 months (mean ± S.D.) with the thyrostatic dosage adjusted to maintain serum TSH concentration in the normal range (0.3–4.0 mU/l). Patients with drug reactions to methimazole (gastrointestinal complaints; n = 4, maculopapular skin rashes; n = 7) were switched to propylthiouracil and were able to finish the study without any further side-effects.
After 9.0 ± 2.5 months patients were randomly assigned to one of three groups. Group 1 (n = 44) stopped thyrostatic treatment with methimazole and was followed every 4–6 weeks. Groups 2 (n = 39) and 3 (n = 31) continued with 25 μg T3 twice daily (not at night) for a further 6 months with either a fixed dose of 10 mg methimazole daily (group 2) or without methimazole (group 3). The T3 dose was kept variable so that the serum TSH was suppressed (<0.1 mU/l) and did not exceed 75 μg daily in any patient. Side-effects of the T3 medication were noted in ten patients (group 2: palpitations: n = 2, light-headedness: n = 1; and group 3: palpitations: n = 5, diarrhoea: n = 1, weight instability: n = 1) but were not felt so disturbing to the patient as to discontinue the study medication. No atrial fibrillation occurred in the patients with palpitations. No differences in the obtained variables were observed between the groups at baseline (Table 1).

Relapse was defined as a rise of TT4 (normal: 5.0–11.2 μg/dl) or of the thyroid function index (TFI; normal: 0.86–1.12) in patients on estrogens above the upper limit of normal in groups 2 and 3, or as an increase of TT4 and the TFI above 11.2 μg/dl and 1.12 respectively, together with TSH suppression in group 1.

Ophthalmopathy was followed by a clinical score (19) which recorded the highest manifestation in grade from 1–6 (1 = signs and symptoms only; 2 = soft-tissue involvement with signs and symptoms; 3 = proptosis 3 mm or more in excess of upper normal limit, with or without symptoms; 4 = extraocular muscle involvement; 5 = corneal involvement; 6 = vision loss). In addition, we recorded use of cigarettes (average number per day) and thyroid size by ultrasound using the ellipsoid formula (volume of each lobe in ml = 1/6 antero-posterior diameter in cm × width in cm × length in cm (20)) at diagnosis and subsequently every 6 months throughout the study. None of the patients had significant retrosternal extension of the thyroid gland which would have interfered with ultrasound measurements. To ensure consistency all ultrasound examinations were performed by the same physician (WR) throughout the study. Urinary iodine excretion (21) was determined twice at 3–4 months after diagnosis when the patient’s serum TT3 and TT4 had entered the normal range as well as after discontinuation of the study medication in either the remission phase or during relapse when thyroid function had returned to normal in response to methimazole by both a 24 h urine sample and a spontaneous voiding sample during visits.

All patients gave informed consent for the participation in the study. The protocol was approved by the Ethics Committee of the University of Vienna Medical School.

Laboratory evaluation

Patients were assessed, and serum was obtained 3 weeks after diagnosis, at randomization (i.e. after 9.0 ± 2.5 months of treatment with methimazole) as well as every 4–6 weeks throughout the study. Serum TSH (IRMA, coated tubes, Cedex, France), TT4 and TT3 (RIA, coated tubes, Becton-Dickinson, Baltimore, MD, USA) or TFI (a bioradiometric assay to obtain free T4 concentrations independent of T4-binding globulin concentration) in women on estrogens were measured at every visit. Serum TRAb concentration was determined at the onset of the study and every 6 months thereafter with a commercial kit (TRAK Assay, Brahms, Berlin, Germany; upper limit of the normal range: 9 U/ml; intra- and interassay coefficients of variation: < 5% and 5–8% respectively). Thyroid size was assessed every 6 months by ultrasonography. Urinary iodine excretion was measured by a photometric assay (21) in all patients after thyroid function had returned to normal (roughly 3–4 months after diagnosis) and after discontinuation of study medication (at normal serum TSH concentrations) in 70% of patients.

Statistical analysis

To detect a 30% difference in remission rates between the treatment groups with 90% certainty (β-error: 10%) the number of patients in every group necessary was calculated to be ≥30. The specificity of the study was set at 95% (i.e. α-error: 5% that a difference is detected between groups when there is actually none). Remission rates were analyzed using Kaplan–Meier curves and compared by the Chi square test between groups.

Data are given as mean ± s.d. ANOVA was used for the comparison of means between the three treatment groups and changes from baseline within the groups were compared by paired Student’s t-test. P values of less than 0.05 were considered significant.

Results

Patient characteristics and urinary iodine excretion

One hundred and fourteen (114) of 135 patients (98 female, 16 male; age: 41 ± 12 years) completed the study. No differences were observed in baseline characteristics (Table 1) between the three groups including age, gender, percentage of women on oral contraceptives, serum TT3 concentration, serum TRAb concentration, thyroid size or number of cigarettes per day (applying just to the smokers). At the time of diagnosis, TRAb concentrations were elevated in 82, 77 and 69% (P = NS) of patients in group 1, 2 and 3 respectively. The percentage of patients smoking was lower (P = NS) in group 3 (23%) than in group 1 (45%) and group 2 (36%). The clinical score and percentage of patients with ophthalmopathy were comparable.
No difference was seen in 24 h urinary iodine excretion between relapsed patients (groups 1: 150 ± 103 μg/24 h, 2: 246 ± 204 μg/24 h and 3: 214 ± 81 μg/24 h) and those in remission (groups 1: 187 ± 112 μg/24 h, 2: 150 ± 68 μg/24 h and 3: 197 ± 77 μg/24 h). Almost one-fifth (19/114; 17%) of patients had urinary iodine excretion less than 100 μg/24 h and 9% (ten patients) more than 300 μg/24 h (not different between groups or between patients in remission and those who have relapsed), which suggests low-to-moderate iodine intake in the majority of patients. The second 24 h urinary iodine excretion rate obtained was comparable with the first in the patients with relapse (groups 1: 198 ± 119 μg/24 h, 2: 158 ± 96 μg/24 h and 3: 133 ± 66 μg/24 h) as well as in those in remission (groups 1: 153 ± 66 μg/24 h, 2: 125 ± 59 μg/24 h and 3: 145 ± 61 μg/24 h). Twenty of 79 patients (25%) displayed a second urinary iodine excretion of less than 100 μg/24 h. The same results were obtained when data were corrected for 24 h urinary creatinine excretion.

Thyroid hormone, cigarette smoking, goiter size and endocrine ophthalmopathy

The mean time required for TT4 and TT3 to enter the normal range was 8.5 ± 7.4 weeks and did not differ between the groups (10.8 ± 8.4, 6.2 ± 4.3 and 8.4 ± 8.1 weeks). The dose of methimazole at the time of randomization was 14 ± 9 mg/day and was comparable between the groups (15 ± 7, 13 ± 9 and 15 ± 10 mg/day). Smoking history (percent of patients who were smoking: number of cigarettes per day in those smoking) was different (P < 0.05) in patients in remission at the end of their follow-up (18%; 8 ± 7 cigarettes/day) from that of patients who relapsed (43%; 19 ± 10 cigarettes/day) but not significantly different for all groups at baseline. Smoking history did not allow prediction of remission, irrespective of treatment group.

Thyroid enlargement – volume >18 ml in women and >25 ml in men (22) – at baseline was noted in 61% of the patients and did not differ at any time between the groups or between patients in remission and in relapse.

The prevalence of endocrine ophthalmopathy decreased (P < 0.05) in patients in remission (5, 0 and 11% of patients with scores 2.0 ± 1.2, 0 and 1.5 ± 1 in groups 1, 2 and 3 respectively) compared with baseline (19, 9 and 28% of patients with scores 2.0 ± 0.8, 1.8 ± 0.8 and 1.7 ± 0.6 in groups 1, 2 and 3 respectively). The frequency of eye changes after recurrence of disease was comparable in group 1 (30 vs 42%), reduced in group 2 (18 vs 53%) and greater in group 3 (62 vs 31%) than at baseline. There was a trend to less severe ophthalmopathy with time in any group, irrespective of remission or relapse.

Serum TRAb (Fig. 1)

Mean serum TRAb concentrations at baseline were comparable in groups 1, 2 and 3 (Table 1). Patients in remission showed a persistent decrease in TRAb (P < 0.01) compared with baseline (77% with normal serum TRAb concentrations by month 6 after the initiation of antithyroid therapy), which is in contrast (P < 0.05) to patients who relapsed (38% with normal serum TRAb concentrations by month 6).

Relapse of hyperthyroidism

After a mean follow-up of 16 months (range: 12–31 months), 52, 44 and 42% of the patients relapsed in groups 1, 2 and 3 respectively. Serum TSH was not detectable in 82% of the patients of groups 2 and 3...
during all of their monthly visits when treated by methimazole plus T3 (group 2) or T3 alone (group 3). The cumulative percentages of patients who relapsed over time in each group are shown in Fig. 2. The displayed right shift of the curve of group 2 (methimazole and T3) is explained by the 6 months longer treatment with antithyroid drugs compared with groups 1 and 3.

After relapse, 46% of patients continued on thyrostatic therapy (48, 41 and 54% in groups 1, 2 and 3 respectively), 26% opted for surgery (18, 35 and 31% in groups 1, 2 and 3 respectively) and 6% for radioiodine treatment (9, 0 and 8% in groups 1, 2 and 3 respectively). All patients on antithyroid drugs were euthyroid when last seen. Two patients decided not to be treated at all after the end of their follow-up (47 and 36 months after first diagnosis respectively) and remained hyperthyroid.

**Discussion**

Graves' disease is a chronic disorder remitting in response to treatment and relapsing thereafter. The disease is thought to be due to disturbed immune regulation, the etiological cause of which remains unknown. One or more TRAbs are thought to be pathogenetically linked to the autonomous overproduction of thyroid hormones (1). Long-term remission rates (up to 10–15 years) after the first episode of hyperthyroidism occur in 20–60% of patients (5, 13, 23, 24). Remission must not be confused with permanent lifelong cure, which has been deemed unlikely to occur if only the follow-up period were long enough (25). High iodine intake has been suggested to be associated with increased relapse rates in patients treated with antithyroid drugs alone (16–18). In addition, results of iodine substitution therapy of patients with diffuse non-toxic goiter suggest that there may be an adverse effect of iodine on thyroid autoimmunity (26). We therefore chose to include urinary iodine excretion rate as an additional outcome-determining variable. On the other hand, prolonged duration of treatment up to 18 months (27) and high doses of antithyroid drugs (28, 29) have been claimed to be beneficial because of their suggested (30) but unconfirmed (31) immunomodulatory function. It is of note that short-term therapy (32, 33) as well as both high- and low-dose thionamide therapy have led to comparable remission rates, however (34).

Putting the thyroid at rest by keeping serum TSH concentrations completely suppressed for an arbitrarily defined period of time by exogenous administration of thyroid hormone was reported to reduce relapse rates by more than 90% (6, 7). The underlying pathogenetic mechanism was related to beneficial effects of T4 and/or lack of TSH stimulation on the autoimmune process (35). The possibility of administering high doses of

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**Figure 2** The cumulative percent of patients with Graves' disease who relapsed as a function of the time after randomization. The number of patients 'at risk' for relapse at a particular time point is depicted above the horizontal axis. Group 2 patients by study design received thyrostatic drug treatment for 6 months longer than those in group 1 and 3. This explains the lower cumulative relapse rate observed from 3 to 8 months after randomization in group 2 compared with the other groups.
thionamide drugs with added exogenous T4 not leading to iatrogenic hypothyroidism has been implemented as well (36).

Group 2 patients by study design received thyrostatic drug treatment for 6 months longer than those in group 1 and group 3. This explains the lower cumulative relapse rate observed from 3 to 8 months after randomization in group 2 compared with the other groups. Comparing the effects of additional T3 on the remission rate in methimazole-treated patients with Graves’ disease we observed remissions (range: 48–58%) that did not differ between groups 1 to 3 (Fig. 2). We were thus unable to confirm the results of the initial report on combined therapy (6) which described a relapse rate of only 1.7% compared with 34.7% in patients without added thyroid hormone. The failure to detect the statistically committed 30% difference in relapse rates between the treatment groups by our investigation is in keeping with the results of several other studies (10–15) that have been reported with equal and less ‘power’ while our study was in progress. As to commenting on the selection of T3 rather than T4 for the goal of TSH suppression, it is of note that more than 80% of patients in group 2 and 3 had serum TSH lower than 0.1 μU/ml on all of their monthly visits during the study period. So T3 was at least as effective as T4 in suppressing serum TSH. One reason that the form of treatment has been said to modify the natural history of Graves’ hyperthyroidism was that remission rates of about 40% were achieved with methimazole compared with 15–20% with propranolol alone (37). Thus, if we assume one therapy to be superior over another because of its influence on the natural disease process, we would probably have to look for a 20 or 25% improvement in long-term remission. This, in turn, would even necessitate a sample size of 80 or 125 patients respectively, per treatment arm, assuming β-error (probability of not detecting a difference when there is actually one) and α-error (probability of detecting a difference when there is actually none) to be 10 and 5% respectively (38).

In two editorial notes, iodine intake has been suggested as an explanation why treatment with exogenous thyroid hormones might work better in Japan than in the USA and Europe (36, 39). Not all studies from Japan (11), however, have shown a beneficial effect of combination therapy which has been related to the lack of suppression on the TRAb production of not-detected serum TSH concentrations induced by exogenous thyroid hormone. As to the contention that high iodine intake increases the danger of relapse of hyperthyroidism in patients with Graves’ disease, it seems noteworthy that urinary iodine excretion was low to moderate in our patients (185 ± 115 and 149 ± 78 μg/day in the two 24 h collections respectively) of whom 25% of patients excreted even less than < 100 μg iodine/24 h irrespective of the prevalence of remission or relapse. The observed urinary iodine excretion is in line with that observed in the local Austrian euthyroid population (40). The comparison of our overall remission rate of 54% with that of others (Table 2) suggests that low iodine intake indeed promotes higher remission rates of Graves’ disease than higher iodine exposure.

Neither serum concentrations of TT3, serum TRAb nor clinical features consistently predicted remission in our study although small goiter or a striking decrease in its size have been suggested to be such predictors (34, 41). While thyroid size remained the same throughout our study, irrespective of group or remission status of the patient, serum TRAb concentrations failed to parallel normalization of thyroid hormone concentrations (Fig. 1) in relapsing patients. The lack of TRAb returning to normal by month 6 after initiation of

**Table 2** Relapse rate and iodine-status of patients in combination therapy studies.

<table>
<thead>
<tr>
<th>Authors (origin)</th>
<th>Number of patients followed</th>
<th>Mean follow-up (months)</th>
<th>Overall relapse (%)</th>
<th>Mean urinary iodine excretion (μg/24 h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hashizume et al. (6) (Japan)</td>
<td>109</td>
<td>36</td>
<td>16</td>
<td>Neither studied nor discussed*</td>
</tr>
<tr>
<td>Edmonds &amp; Tellez (10) (UK)</td>
<td>70</td>
<td>24</td>
<td>59</td>
<td>Neither studied nor discussed*</td>
</tr>
<tr>
<td>Tamai et al. (11) (Japan)</td>
<td>105</td>
<td>12</td>
<td>32</td>
<td>Neither studied nor discussed*</td>
</tr>
<tr>
<td>McIver et al. (12) (UK)</td>
<td>23</td>
<td>18</td>
<td>35</td>
<td>Not studied (160)³</td>
</tr>
<tr>
<td>Pfeilschifter &amp; Ziegler (15) (Germany)</td>
<td>50</td>
<td>12</td>
<td>44</td>
<td>Not studied (&lt; 100)³</td>
</tr>
<tr>
<td>Lucas et al. (13) (Spain)</td>
<td>60</td>
<td>60</td>
<td>63</td>
<td>Not studied (&gt; 300)³</td>
</tr>
<tr>
<td>Rittmaster et al. (14) (USA)</td>
<td>149</td>
<td>27</td>
<td>58</td>
<td>214 (measured in 39% of patients)</td>
</tr>
<tr>
<td>Raber et al. (present study) (Austria)</td>
<td>114</td>
<td>16</td>
<td>46</td>
<td>185/149 (measured twice in 100%/70% of patients respectively)</td>
</tr>
</tbody>
</table>

1 Number of patients who were followed up rather than the number of those included in the study were deemed important.
2 Follow-up after stopping antithyroid medication.
3 Urinary iodine excretion not studied, but cited regional values reported.
4 Average daily iodine excretion in Japan: 450 μg/24 h (from reference 43).
antithyroid therapy, however, was only 62% specific for a relapse of hyperthyroidism, which is in keeping with the results obtained by others (42). In contrast, mean serum TRAb concentrations returned to normal and remained within the normal range until the end of follow-up in those in remission.

In conclusion, our study failed to provide evidence for improved remission rates by added T3 in newly diagnosed Graves’ disease treated with methimazole. In addition, no predictor of disease recurrence prior to the start of therapy could be identified, while low-to-moderate urinary iodine excretion suggests high overall remission rates.

Acknowledgement

This study was supported by grants from Diachrom, Vienna and Sandoz, Austria, which are gratefully acknowledged.

References


Received 7 April 1999
Accepted 18 August 1999