Effects of high and low doses of methimazole in patients with Graves' thyrotoxicosis

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Abstract. In spite of the long-established use of antithyroid drugs, there are many unsettled questions connected with this treatment of Graves' disease. There is a lack of controlled prospective trials studying the results of antithyroid drug therapy while considering the many variables such as disease heterogeneity, regional differences, drug dosage and duration of treatment. Therefore, a multicenter study has been set up in order to compare the effects of two fixed doses of methimazole (10 vs 40 mg) with thyroid hormone supplementation on the clinical, biochemical and immunological course of Graves' disease and on remission rates. Experience accumulated so far suggests that treatment is safe using either 10 or 40 mg of methimazole. While there is a tendency for an advantage of the higher dose within the first weeks (higher effectiveness in controlling hyperthyroidism), this difference is not significant. The impact of dosage on remission rates remains to be shown.

A survey on hyperthyroidism (HT) in Europe conducted between 1981 and 1982 has shown that the majority of patients were treated with antithyroid drugs (AD). Similar results have been obtained from the Symposium on Treatment of hyperthyroidism due to Graves' disease during the ETA Meeting on July 1st, 1986 at Stockholm.

Although large differences were evident between countries, AD appeared to be the treatment of choice for most patients. Still, the modalities of AD treatment are controversial. Long-term remission rates after AD are often unsatisfactory, and in any case, they are rather unpredictable. There is no agreement on dose or duration of AD, or on the selection of patients most suited for this form of treatment, or on methods to predict remission or relapse probability. In view of recent insight into the potential immunosuppressive actions of AD (Kendall-Taylor 1984; Ratanachaya-vong & McGregor 1985; Weetman et al. 1984) the dose aspect has gained importance. Since small doses of AD have been shown to be effective in the initial control of HT, at least in a majority of patients (Low et al. 1981; Shiroozu et al. 1986; Seidel et al. 1984; McCruden et al. 1985), their remission, and reductions in drug dose may well have to be paid for by a reduction in remission rates. Investigating this dose problem is the main object of the European Multicenter Trial which addresses both the short-term and the long-term effectiveness of AD.
Materials and Methods

Aims of the European Multicenter Trial

This trial started in 1984 on the initiative of the late Professor Crooks from Dundee and was preceded by a survey on HT at the participating centres. This survey showed that most patients seen were Graves' patients, although with local differences, that most of them were going to be treated by AD and that many differences (e.g. in goitre size and thyroid hormone levels) could be explained on the basis of differences in iodine supply. In this trial, we want to allocate patients randomly to treatment with two different fixed dosages of methimazole with thyroxine supplementation. All information related to patient classification, iodine contamination, is to be collected centrally. As a result, the diagnosis of Graves' disease is based on central evaluation of eye signs and determination of TBIAb. All patients suitable for treatment with AD are to be entered into the trial unless excluded by age (below 16 or above 70 years), pregnancy, indications for ablative treatment, previous treatment with antithyroid drugs within the last 12 months or concomitant immunosuppressive therapy.

Design of the trial

A flow-sheet of the trial is given in Table 3. Patients are treated with either 10 or 40 mg of methimazole for 1 year, while the euthyroid state is maintained by the addition of l-thyroxine. Before starting therapy, samples are obtained for estimation of TBIAb, thyroid autoantibodies and urinary iodide, and a 20 min uptake is performed (not compulsory). Patients may be withdrawn at any time for reasons of non-compilance, personal reasons, pregnancy, adverse reactions or failure to respond to the drug. Patients not responding to 10 mg of methimazole within 12 weeks may be switched over to the 40 mg group; however, this has been a very rare event until now. Treatment is stopped after 1 year, a suppression test is performed, and TBIAb are measured again. The patient is then followed-up for another year to watch for a recurrency.

Results

Present state of patient recruitment

By the end of August, 1986, 207 patients have been entered into the trial, 86% were women, and 14% were men. 103 patients are taking 10, and 104 patients are taking 40 mg of methimazole. 67 patients have completed the first year, and only 1 patient the second year of observation (Fig. 1). Five patients relapsed in the low-dose group, and 2 in the high-dose group. Fig. 2 gives the age distribution of the patients which is typical for Graves' disease, with a peak in the fourth decade.

Achievement of euthyroidism

A crucial problem was whether the 10 mg dose would leave a substantial number of patients hyperthyroid. However, after 3 weeks of therapy,
already 53 out of 81 patients treated with 10 mg, and 63 out of 83 patients treated with 40 mg of methimazole were euthyroid, corresponding to 65 and 76% (Fig. 3). After 6 weeks, these figures were 82 and 90%. The differences just fail to reach statistical significance ($\chi^2 = 2.17$).

20-min thyroid uptake

The uptake was $21.3 \pm 3.2\%$ (mean $\pm$ SEM) in 19 patients on 10 mg of methimazole, and decreased with treatment to $11.6 \pm 2.4\%$. In 26 patients on 40 mg, uptake decreased from $23.1 \pm 3.4\%$ to $9.7 \pm 1.6\%$ (Fig. 4). The decreases in uptake were significant ($P = 0.002$ and 0.001, respectively, by Wilcoxon's matched pairs signed rank test). The differences between the two doses have not been tested due to the fact that they may have been influenced by differences in the dose of thyroxine supplementation. Defining an uptake of less than 10% as a 'positive suppression test' after comple-
CHANGES IN UPTAKE DURING TREATMENT

Fig. 3.
Percentage of biochemically euthyroid patients after 3 and 6 weeks' treatment with either 10 or 40 mg of methimazole.

tion of the one year AD course, this goal was achieved in 9 of our 19 patients on 10 and in 16 out of 26 patients on 40 mg of methimazole. These results are not significant.

Side effects
These were reported in 14 patients on 10 and in 24 patients on 40 mg of methimazole. Three patients on 10 and 12 on 40 mg of methimazole were withdrawn because of side-effects. Pruritus was most frequent (n = 16), followed by rash (n = 10) and a variety of other symptoms, the relationship of which with AD were not always quite clear-cut. There was no agranulocytosis.

Discussion
The dose of antithyroid drugs is one out of several variables in AD treatment. A provisional list of variables which have been shown or suggested to be important for the outcome of treatment with AD includes:

1) Disease factors: goitre size and TBIAb or TSI.
2) Individual factors: HLA status.
3) Environmental factors: iodine content of food and iodine contamination.
4) Treatment factors: dose of AD and duration of treatment.

The remission rates in patients with different goitre sizes have been studied by Laurberg et al.

Fig. 4.
Decrease in 20 min-thyroid uptake after 1 year of treatment with either 10 or 40 mg of methimazole. The decreases are significant for both dosages, but the differences between the two doses are not significant.
Table 1.
Remission rates after antithyroid treatment (estimates by life-table analysis, mean and standard errors of calculated remission rates) and observed remission rates with 95% confidence intervals in relationship to goitre size (modified after Laurberg et al. 1986).

<table>
<thead>
<tr>
<th>Goitre size</th>
<th>No goitre</th>
<th>Small 20–40 g</th>
<th>Big &gt; 40 g</th>
<th>Multinodular goitre</th>
</tr>
</thead>
<tbody>
<tr>
<td>Remission rate, % (life-table) ± SEM</td>
<td>82.5 ± 15.4</td>
<td>71.5 ± 7.8</td>
<td>37.5 ± 11.1</td>
<td>15.5 ± 10.1</td>
</tr>
<tr>
<td>No. of patients</td>
<td>19</td>
<td>57</td>
<td>23</td>
<td>25</td>
</tr>
<tr>
<td>Observed relapses</td>
<td>3</td>
<td>18</td>
<td>14</td>
<td>22</td>
</tr>
<tr>
<td>Observed remissions</td>
<td>84</td>
<td>68</td>
<td>39</td>
<td>22</td>
</tr>
<tr>
<td>95% confidence limits, %</td>
<td>60–97</td>
<td>55–80</td>
<td>20–61</td>
<td>3–31</td>
</tr>
</tbody>
</table>

(1986). The results are shown in Table 1. With increasing size of the gland, remission rates estimated by life-table analysis decline from 82 to 37%. These results agree well with clinical experience of thyroidologists: a large goitre in a young patient with Graves' disease does not permit much hope for lasting remission, and in an old patient and non-immune disease, a large long-standing goitre may indicate a substantial amount of autonomous tissue with is not cured by AD. The exception may be patients with iodine contamination who experience a short phase of hyperthyroidism and go back into latent HT, when they regain their usual state of iodine deficiency.

Improvement of the HT of Graves' disease is frequently associated with a fall in TSH-binding inhibiting immunoglobulins (TBIAb) and thyroid-stimulating immunoglobulins (TSI), which is thought to be an effect of AD (Ratanachaiyavong & McGregor 1985). However, although these immunoglobulins certainly play a role in the pathogenesis of thyrotoxicosis, their value as a prognostic test for long-term remission appears to be limited. The same holds true for HLA typing which does not predict the outcome of antithyroid drug treatment.

Among environmental factors, the iodine balance undoubtedly plays a role for the initial response to AD which may be prolonged in countries with high iodine supply, and may also be prolonged in iodine-contaminated individuals. Azizi (1985) studied the initial response to antithyroid drugs in Boston and in Tehran and showed that this response was delayed in Boston which may be a result of the high iodine content of food in the US. Emrich & Paulenz (1985) showed that in iodine-contaminated patients (urinary iodide above 250 µg/g creatinine), the time needed for recompensation was prolonged, and was not related to MMI dose. In individuals excreting less than 50 µg of iodine/g of creatinine, the biochemical normalization was slower in patients receiving a low dose of MMI, i.e. in the iodine-depleted state, there was a relationship between MMI dose and time for recompensation.

There is evidence that AD alter the course of Graves' disease (Kendall-Taylor 1984; Weetman et al. 1984), i.e. that remission rates after treatment with thioureylene drugs are higher than the rates of spontaneous remissions (which are traditionally extrapolated from remission rates after beta-blocking agents). The type of HT is important because inclusion of non-immune forms of HT as well as Hashitoxicosis and other forms of thyroiditis and transient forms of HT will result in a misleading figure of remission rates. When, in Graves' disease, AD act as immunomodulatory agents within the thyroid, then dose and duration of treatment must be most important for the outcome.

Duration of treatment varies, and a relationship has been demonstrated between duration of therapy and remission rate. Schifferdecker & Schöffling (1985) have performed a review of the literature showing that, on the average, remission rate increases when treatment is continued for 2 years or more (Table 2). However, this takes no account of disease heterogeneity and differences in iodine supply or other possible geographical factors which all may contribute to differences in outcome.
come. A prospective study showing a significant increase in remission rates after treatment for 18 months compared to 6 months has been presented by Allanic et al. (1986).

There exists only one larger study which compares different dosages of AD, although not prospectively, published by Romaldini et al. (1983). They treated two groups of patients with either high or low doses of MMi or PTU. The high dose was 60 mg of methimazole or about 700 mg of PTU, and the low dose was about 15 mg of methimazole or 180 mg of PTU. Mean follow-up time was 42 ± 14 months. There was a significant difference in remission rates, of methimazole or about 700 mg of PTU, and the low dose was about 15 mg of methimazole or 180 mg of PTU. Mean follow-up time was 42 ± 14 months. There was a significant difference in remission rates, namely, 75% in the high-dose group, and 41% in the low-dose group. In the two groups, goitre size, immunological findings, presence of eye signs and duration of treatment were comparable, although no reason was given for the difference in treatment in the two groups. It remains to be shown if the prospective trial presented here will confirm those results in spite of the somewhat lower doses of methimazole used by us.

References


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<table>
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<tr>
<th>Duration of therapy</th>
<th>Remission rates (%)</th>
<th>95% confidence limits</th>
</tr>
</thead>
<tbody>
<tr>
<td>Less than 1 year</td>
<td>33</td>
<td>27–40</td>
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<tr>
<td>1 year</td>
<td>40</td>
<td>35–48</td>
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<td>1–2 years</td>
<td>46</td>
<td>41–51</td>
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<tr>
<td>2 years</td>
<td>52</td>
<td>47–58</td>
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<tr>
<td>More than 2 years</td>
<td>57</td>
<td>50–64</td>
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</table>

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