

LACK OF EFFECT OF THYROXINE IN PATIENTS WITH GRAVES' HYPERTHYROIDISM WHO ARE TREATED WITH AN ANTITHYROID DRUG

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Abstract Background. Antithyroid drugs are effective in patients with hyperthyroidism due to Graves' disease, but the rate of recurrence after treatment is high. In a recent Japanese study, adjunctive treatment with thyroxine (T_4) was associated with a recurrence rate 20 times lower than that among patients who received only an antithyroid drug. If these results are confirmed, combined therapy with an antithyroid drug and T_4 might become the treatment of choice for all patients with Graves' hyperthyroidism.

Methods. We treated 111 patients (89 women and 22 men) who had Graves' hyperthyroidism. All patients initially received 40 mg of carbimazole daily for one month. Then one group received carbimazole alone for 17 months (52 patients), and the other group received carbimazole plus T_4 for 17 months and T_4 alone for 18 months (59 patients). In the carbimazole group, the dose was adjusted after one month to maintain a normal serum thyrotropin concentration. In the carbimazole- T_4 group, the dose of carbimazole was not changed, but 100 μg of T_4 per day

was added to the regimen and the dose was adjusted to maintain an undetectable serum thyrotropin concentration ($<0.04 \mu\text{U}$ per milliliter).

Results. At the time of our analysis, 53 of the 111 patients had completed at least 3 months of follow-up (median, 12 months) after carbimazole was withdrawn. Hyperthyroidism recurred in eight patients in each group after a mean ($\pm\text{SD}$) of 6 ± 4 months in the carbimazole group and 7 ± 4 months in the carbimazole- T_4 group. There was no difference between the recurrence rates in the two groups, despite the fact that serum thyrotropin concentrations were undetectable in 73 percent of patients in the carbimazole- T_4 group on at least 75 percent of their visits.

Conclusions. The administration of T_4 to patients with Graves' disease during carbimazole treatment and after its withdrawal neither delays nor prevents the recurrence of hyperthyroidism. (N Engl J Med 1996;334:220-4.)

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ANTITHYROID drugs are effective in controlling hyperthyroidism because they inhibit thyroid hormone production. In patients with hyperthyroidism caused by Graves' disease, these drugs may also have an immunosuppressive effect, causing a decrease in the serum concentrations of thyrotropin-receptor antibodies.¹ The main disadvantage of antithyroid drug therapy is that the rate of recurrence after treatment is stopped varies widely, from 25 percent to 90 percent.^{2,3} Factors that affect the recurrence rate include the dosage and the duration of treatment.⁴ One reason for using high doses of antithyroid drugs, which must be combined with thyroid hormone if hypothyroidism is to be averted, is the belief that the postulated immunosuppressive effect may be related to the dose. For example, in one study the recurrence rate was 55 percent among patients treated with an antithyroid drug alone and 25 percent among those given combined therapy.⁵ In a large, prospective, multicenter European trial,⁶ however, combination therapy was no more effective than antithyroid treatment alone.

The high rates of recurrence have led many physicians to favor subtotal thyroidectomy or therapy with radioactive iodine for patients with Graves' hyperthyroidism. When Hashizume et al.⁷ reported in 1991 that the rate of recurrence of hyperthyroidism in Japanese patients could be reduced from 35 percent to less than 2 percent by 18 months of treatment with methimazole, with thyroxine (T_4) added after the first six months and continued for three years after the meth-

imazole was discontinued, this finding was considered by many the most important development in the management of Graves' hyperthyroidism in many years. If the results of Hashizume et al. were confirmed in different ethnic groups, this combined regimen might well become the treatment of choice for patients with Graves' hyperthyroidism. We undertook this study to determine the efficacy of the combination of an antithyroid drug and T_4 in another group of patients.

METHODS

We studied 111 consecutive, previously untreated patients with hyperthyroidism due to Graves' disease. The diagnosis of hyperthyroidism was made on clinical grounds and on the basis of elevated concentrations of free T_4 and total triiodothyronine (T_3) and undetectable serum thyrotropin concentrations ($<0.04 \mu\text{U}$ per milliliter). The determination that Graves' disease was the cause of the hyperthyroidism was based on the presence of diffuse goiter, ophthalmopathy or pretibial myxedema, or detectable serum concentrations of thyrotropin-receptor antibodies (detected in 88 percent of the patients). All the patients had a normal or high thyroidal uptake of iodine 131, and technetium 99m pertechnetate imaging showed a diffuse pattern of uptake. All patients gave informed consent for their participation in the study.

All the patients were treated initially with 20 mg of carbimazole twice daily (40 mg per day) for one month. They were then randomly assigned to receive carbimazole alone (52 patients) or carbimazole plus T_4 (59 patients). In the carbimazole group, the dose of carbimazole was adjusted as necessary to achieve normal serum concentrations of thyrotropin, free T_4 , and T_3 ; the patients did not receive a placebo in place of T_4 . The patients in the carbimazole- T_4 group continued to receive 20 mg of carbimazole twice daily, but T_4 was added at an initial dose of 100 μg daily. The dose of T_4 was adjusted as necessary to achieve an undetectable serum thyrotropin concentration ($<0.04 \mu\text{U}$ per milliliter). When this degree of suppression of serum thyrotropin was achieved, serum free T_4 concentrations were in the upper part of the normal reference range or slightly high and serum T_3 concentrations were normal. All patients in both groups received carbimazole for 18 months. T_4 was given to patients in the carbimazole- T_4 group for 35 months — with carbimazole for 17 months and

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then for 18 months after carbimazole was discontinued. The dose of T₄ was not changed when carbimazole was discontinued.

The patients were examined clinically, and blood was collected for estimation of the serum concentrations of thyrotropin, free T₄, T₃, and thyrotropin-receptor antibodies at the initial visit, at one month, at three months, and at three-month intervals thereafter for up to three years. All three physicians participating in the study were aware of the group assignment of the patients; to ensure consistency, adjustments to therapy were determined by a single physician.

Treatment was deemed to have failed in the patients in the carbimazole group if hyperthyroidism recurred after carbimazole was withdrawn. In those in the carbimazole-T₄ group, treatment was considered to have failed if there was clinical and biochemical evidence of hyperthyroidism while the patient was taking T₄ alone.

Measurement of Serum Thyrotropin, T₄, T₃, and Thyrotropin-Receptor Antibodies

Serum thyrotropin was measured by an immunochemiluminometric assay (Amerlite TSH-30, Kodak Clinical Diagnostics, Amersham, United Kingdom), with a functional limit of detection of 0.04 μU per milliliter⁸ and a coefficient of variation of less than 10 percent over the range of 0.04 to 100 μU per milliliter (normal range, 0.15 to 3.5). The serum thyrotropin concentration was defined as suppressed if the value was below 0.04 μU per milliliter; undetectable values were assigned a value of 0.04 μU per milliliter for purposes of analysis.

Free T₄ and T₃ were measured in serum with commercial kits (Amerlite-MAB and Amerlite Total T₃, Kodak Clinical Diagnostics). The interassay coefficients of variation were less than 10 percent over the ranges measured.

Serum thyrotropin-receptor antibodies were measured by an assay in which the capacity of the patient's serum to inhibit the binding of ¹²⁵I-labeled thyrotropin to its receptors was tested (RSR, Cardiff, United Kingdom); in this assay, biologically active thyrotropin standardized against Medical Research Council Long-Acting Thyroid Stimulator Standard B was used. A value of 7 U per liter for serum thyrotropin-receptor antibodies was defined as the upper limit of normal. Values greater than this had a sensitivity of 81 percent and a specificity of 96 percent for the diagnosis of Graves' hyperthyroidism in our laboratory.

Statistical Analysis

Statistical analysis was performed with the Statistical Package for the Social Sciences (SPSS, Chicago). All statistical tests were two-tailed. The results are given as means ±SD unless otherwise stated. The Mann-Whitney U test was used to assess differences between groups, and the Wilcoxon paired signed-rank test to assess differences within groups. The rates of decrease in the serum levels of thyrotropin-receptor antibodies in the two groups were compared with the Hollander test for parallelism after logarithmic transformation of the results. Rates of recurrence were determined by life-table analysis, and the differences between the groups were assessed with the Gehan statistic.

RESULTS

The characteristics of the two groups before treatment were similar (Table 1). Ten patients in each group were withdrawn from the study: five because of the side effects of the drug (urticaria, arthralgia, or nausea), six because of noncompliance, and nine because of a change in residence. At the time of the analysis, 53 patients had completed carbimazole treatment and at least three months of follow-up thereafter. Forty-five of the 53 patients had been followed for six months (of the remainder, 6 had recurrences and 2 had less than six months of follow-up). Of the 45, 30

had been followed for 12 months (5 of the remainder had recurrences and 10 had less than 12 months of follow-up); 23 had been followed for 18 months (5 of the remainder had recurrences and 2 had follow-up of less than 18 months). The median follow-up period was 12 months.

Doses of Carbimazole and T₄

The dose of carbimazole required to maintain normal serum thyrotropin, free T₄, and T₃ concentrations in the patients in the carbimazole group fell during the first six months and then reached a plateau at 10±5 mg daily. By design, the dose was 40 mg daily throughout the study period in the carbimazole-T₄ group; in this group the daily dose of T₄ required to maintain an undetectable serum thyrotropin concentration was 167±41 μg.

Effects of Treatment on Serum Thyroid Hormone and Thyrotropin Concentrations

During the first month of treatment with 40 mg of carbimazole per day, the mean serum free T₄ concentration fell from 5.0±3.0 to 1.4±1.3 ng per deciliter (from 64±39 to 18±17 pmol per liter) (Fig. 1), and the serum T₃ concentration fell from 409±195 to 150±65 ng per deciliter (from 6.3±3.0 to 2.3±1.0 nmol per liter). There was no difference in the rate of decrease in the concentration of either hormone between patients in the carbimazole group and those in the carbimazole-T₄ group. Thereafter, the mean serum free T₄ concentrations were consistently higher in the carbimazole-T₄ group (Fig. 1). There was no difference in serum T₃ concentrations between the groups at any time.

The mean serum thyrotropin concentration in the carbimazole group after one month was 0.31 μU per milliliter (thyrotropin was undetectable in 87 percent of the patients). The value increased to a peak of 3.0 μU per milliliter at three months, after which it ranged from 1.2 to 1.9 μU per milliliter until carbimazole was discontinued. The proportion of patients with an undetectable serum thyrotropin concentration at these times varied from 7 to 10 percent. Overt biochemical (but asymptomatic) hypothyroidism (indicated by a low serum free T₄ concentration and an increased serum thyrotropin concentration) occurred in 13 patients at three months but was corrected by a reduction in the dose of carbimazole.

In the carbimazole-T₄ group, overt biochemical hy-

Table 1. Characteristics of the Patients with Graves' Hyperthyroidism before Treatment.*

TREATMENT GROUP	NO. OF PATIENTS	SEX (F/M)	AGE (YR)	¹³¹ I UPTAKE (%)	SERUM THYROTROPIN (μU/ml)	SERUM FREE T ₄ (ng/dl)	SERUM T ₃ (ng/dl)	SERUM TRAb (U/liter)
Carbimazole	52	41/11	33±9	52±18	<0.04	4.9±1.9	403±169	23.4±27.5
Carbimazole-T ₄	59	48/11	36±10	54±17	<0.04	5.1±1.9	416±182	30.6±33.6
Normal range					0.15-3.5	0.8-2.1	65-169	<7

*Plus-minus values are means ±SD. Iodine uptake was measured three hours after the oral administration of 5.4 μCi (200 kBq) of iodine 131 (¹³¹I) and expressed as a percentage of the administered dose. To convert values for serum free T₄ to picomoles per liter, multiply by 12.87; to convert values for total T₃ to nanomoles per liter, multiply by 0.0154. TRAb denotes thyrotropin-receptor antibodies.

pothyroidism (also asymptomatic) occurred in only two patients at three months and was corrected by increasing the dose of T_4 . Serum thyrotropin concentrations were undetectable in 73 percent of the patients on at least 75 percent of their visits during carbimazole- T_4 therapy. In half the remaining patients, it was not possible to maintain an undetectable serum thyrotropin concentration because of symptoms of hyperthyroidism; these patients continued to receive the maximal tolerated dose of T_4 and are included in the subsequent analysis.

At the first follow-up evaluation, three months after the withdrawal of carbimazole, the mean serum thyrotropin concentrations in the carbimazole group had fallen from 1.9 ± 3.3 to 0.35 ± 0.30 μU per milliliter ($P < 0.001$), but the mean serum free T_4 concentration was virtually unchanged (from 1.2 ± 0.3 to 1.4 ± 0.5 ng per deciliter [16 ± 4 to 18 ± 6 pmol per liter]). In the carbimazole- T_4 group, the mean serum thyrotropin concentration fell from 0.3 ± 0.1 to 0.1 ± 0.04 μU per milliliter ($P = 0.02$), and the mean serum free T_4 con-

centration rose from 2.0 ± 0.2 to 2.5 ± 0.3 ng per deciliter (25.7 ± 2.6 to 32.2 ± 3.9 pmol per liter; $P = 0.03$).

Effect of Treatment on Serum Concentrations of Thyrotropin-Receptor Antibodies

Serum thyrotropin-receptor antibody concentrations fell progressively during the 18 months of carbimazole therapy, from 23.4 ± 28.4 to 3.4 ± 7.3 U per liter in the carbimazole group and from 30.6 ± 35.0 to 5.3 ± 12.1 U per liter in the carbimazole- T_4 group (Fig. 2). There was no difference in mean serum concentrations of thyrotropin-receptor antibodies or in the proportion of patients in whom thyrotropin-receptor antibodies were present between the two groups at the start of carbimazole treatment. Similarly, there was no difference in the rate of decrease in the antibody concentrations during or at the end of carbimazole treatment. After the withdrawal of carbimazole, serum concentrations of thyrotropin-receptor antibodies remained similarly low in both groups.

Recurrence of Hyperthyroidism

Patients at risk for a recurrence of hyperthyroidism were those still being followed up who had not already had relapses. There were 45 such patients at 3 months, 41 at 6 months, 37 at 9 months, 30 at 12 months, 26 at 15 months, and 23 at 18 months.

Eight patients in the carbimazole group had recurrent hyperthyroidism a mean of 6 ± 4 months after the discontinuation of carbimazole, at which time their serum free T_4 concentrations ranged from 2.7 to 7.0 ng per deciliter (34 to 90 pmol per liter), and their serum T_3 concentrations ranged from 195 to 474 ng per deciliter (3.0 to 7.3 nmol per liter). Recurrent hyperthyroidism developed in eight patients in the carbimazole- T_4 group a mean of 7 ± 4 months after the discontinuation of carbimazole and while they were taking thyroxine in a dose that, when given in combination with carbimazole, was associated with a euthyroid state. At the time of recurrence, the serum free T_4 concentrations in these patients ranged from 3.0 to 7.0 ng per deciliter (39 to 90 pmol per liter), and their serum T_3 concentrations ranged from 188 to 630 ng per deciliter (2.9 to 9.7 nmol per liter). All but one of the eight patients with recurrent hyperthyroidism in the carbimazole- T_4 group remained overtly hyperthyroid after the withdrawal of T_4 ; the remaining patient had subclinical hyperthyroidism.

At the time of recurrence, thyrotropin-receptor antibodies could not be detected in serum from four of the eight patients in the carbimazole group and three of the eight patients in the carbimazole- T_4 group. In all those with detectable thyrotropin-receptor antibodies in serum, the concentration at the time of recurrence was less than that at the time of diagnosis. Life-table analysis showed no difference between the rates of relapse in the two groups ($P = 0.41$) (Fig. 3).

DISCUSSION

In contrast to Hashizume et al.,⁷ we found that the addition of T_4 to carbimazole in the treatment of patients

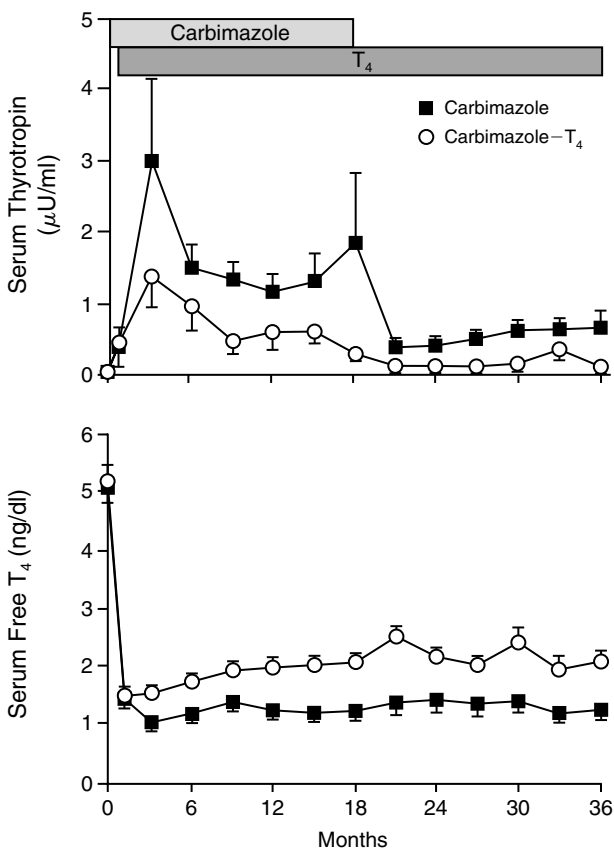


Figure 1. Mean (\pm SE) Serum Free T_4 and Thyrotropin Concentrations in the Carbimazole Group and the Carbimazole- T_4 Group, According to the Length of Time from the Start of the Study.

The normal reference ranges are 0.8 to 2.1 ng per deciliter (10 to 27 pmol per liter) for T_4 and 0.15 to 3.5 μU per milliliter for thyrotropin. The periods of carbimazole treatment in both groups and of T_4 treatment in the carbimazole- T_4 group are indicated by the horizontal bars.

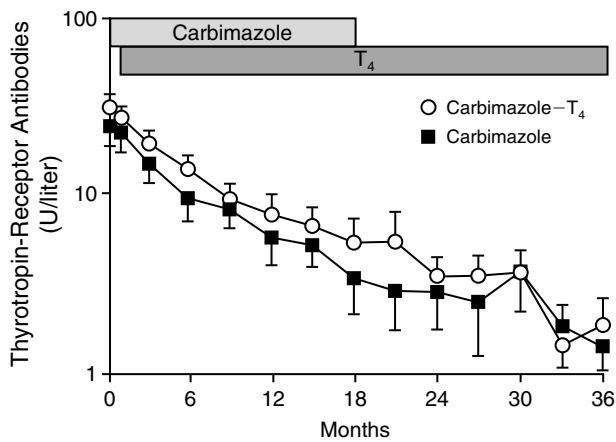


Figure 2. Mean (\pm SE) Serum Concentrations of Thyrotropin-Receptor Antibodies in the Carbimazole Group and the Carbimazole-T₄ Group, According to the Length of Time from the Start of the Study.

The values for thyrotropin-receptor antibodies are plotted on a logarithmic scale. There was no significant difference in mean serum thyrotropin-receptor antibody concentrations between the groups at any time, and the rate of decrease was similar in the two groups. The periods of carbimazole treatment in both groups and of T₄ treatment in the carbimazole-T₄ group are indicated by the horizontal bars.

with Graves' hyperthyroidism and the continued administration of T₄ after carbimazole therapy was stopped did not decrease the rate of recurrence. Although only 53 patients had completed carbimazole therapy at the time of this report, the rates of relapse in the two groups were similar. Even if a small difference between the groups were to become apparent with greater numbers of patients and longer follow-up, the potential benefit of T₄ would be outweighed by the development of symptoms of hyperthyroidism in some of the patients in the carbimazole-T₄ group. In addition, the prolonged suppression of thyrotropin secretion entails the risk of such undesirable effects as atrial fibrillation⁹ and possibly osteoporosis.¹⁰

The rationale for attempting to suppress endogenous thyrotropin secretion was that the release of antigens by the thyroid gland would be inhibited and the immune response modified in such a way as to make the long-term remission of Graves' disease more likely. Serum thyrotropin concentrations were more effectively suppressed in the T₄-treated group in our study than in the Japanese study, yet unlike Hashizume et al., we were unable to demonstrate any additional decrease in serum concentrations of thyrotropin-receptor antibodies in the group treated with carbimazole and T₄, as compared with the group treated with carbimazole alone. Although their study is not directly comparable to ours, Tamai et al. were unable to demonstrate a T₄-induced decrease in persistently elevated serum thyrotropin-receptor antibody concentrations in Japanese patients who had previously been treated with methimazole for 12 months.¹¹

What are the possible explanations for the apparent

discrepancy between the results of our study and that reported by Hashizume et al.⁷ One is differences in the details of treatment and in the choice of drug. For example, Hashizume et al. used methimazole, whereas we used carbimazole. The latter is rapidly converted to methimazole, and there is no evidence that carbimazole is anything other than a precursor of methimazole. Another possible explanation is differences in iodine intake. The average daily intake of iodine in Japan is 470 μ g,¹² about three times that in the United Kingdom,¹³ but — if anything — higher iodine intake is associated with a higher rate of recurrence of hyperthyroidism.¹⁴⁻¹⁶ Given the higher iodine intake in Japan, the rates of recurrence there are relatively low,^{7,17} raising the possibility that in Japanese patients the thyroid gland has in some way become adapted to their higher dietary iodine intake. The initial depletion of thyroidal iodine during antithyroid drug therapy, followed by the suppression of iodine uptake by T₄ in the presence of reduced serum concentrations of thyrotropin-receptor antibodies, might be sufficient to prevent recurrences in the short term in Japanese patients who are inherently resistant to the effects of iodine.

One would expect the organic iodine content of the thyroid glands of Japanese patients with Graves' hyperthyroidism to be greater and their response to antithyroid drugs correspondingly slower than those of the patients in our study. Indeed, this was the case, since doses of 30 mg of methimazole daily were given for six months without inducing hypothyroidism in the Japanese study, before thyroxine or placebo was added. In our patients, carbimazole was given at a dose of 40 mg daily for only one month before it was reduced or T₄ was added to prevent the possible development of hypothyroidism. The patients in the carbimazole-T₄ group received greater doses of antithyroid drug during the 18-month study and received the combination of an antithyroid drug and T₄

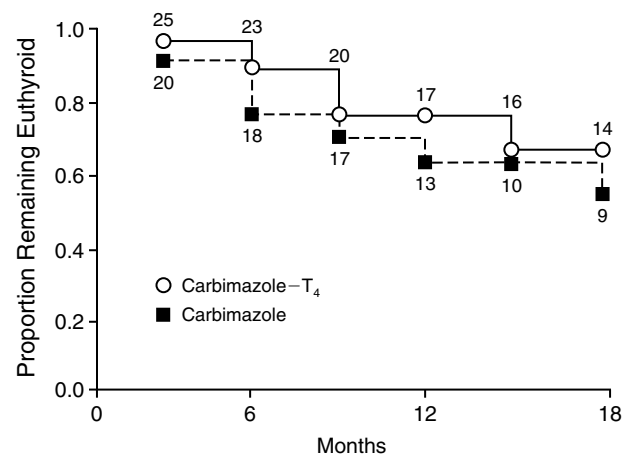


Figure 3. Proportion of Patients Remaining Euthyroid, According to the Length of Time since the End of Carbimazole Treatment.

The numbers above and below the symbols indicate patients at risk for recurrent hyperthyroidism. There was no significant difference in the rates of recurrence in the two groups ($P=0.41$).

for a longer period than their Japanese counterparts (17 vs. 12 months); these variations in dose and timing might have been expected to result in a greater chance of remission among the patients in our study.

There are obviously genetic differences between patients in Japan and the United Kingdom, and it is perhaps naive to assume that the pathogenesis of disease and its response to treatment will be similar in all ethnic groups. Major histocompatibility complex class II antigens (HLA antigens) are an important factor in the development of organ-specific autoimmune disease, of which Graves' disease is an example. Although HLA-B8 and HLA-DR3 are overrepresented among patients with Graves' disease in the United Kingdom, HLA-B35 is overexpressed in Japanese patients.¹⁸ Whether these differences account for variations in the natural history of the hyperthyroidism of Graves' disease is not known.

Whatever the reasons for the differences between the two studies, our inability to confirm the finding of Hashizume et al. that the administration of T₄ reduces the risk of recurrent hyperthyroidism caused by Graves' disease after the discontinuation of antithyroid drug therapy argues against a dose-related immunosuppressive action of carbimazole (and presumably methimazole). Our findings also argue against a role for thyrotropin in maintaining thyroid-antigen expression as an important factor in sustaining Graves' hyperthyroidism. At a practical level, our results provide no evidence that thyroxine increases the efficacy of antithyroid drug therapy for the treatment of patients with hyperthyroidism due to Graves' disease.

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