

Comparison of the Efficacy of Single and Multiple Regimens of Carbimazole in the Treatment of Thyrotoxicosis

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Summary

Carbimazole, in 3 divided daily doses, is commonly prescribed for the treatment of thyrotoxicosis. However, based on its long intra-thyroid half-life, the drug may be effective when used as a single or twice daily dose. This study was undertaken to determine the effect of once, twice or thrice daily doses of carbimazole on thyroid function in patients with thyrotoxicosis.

Seventy previously untreated thyrotoxic patients were randomly allocated to receive carbimazole 30 mg once (group 1), 15 mg twice (group 2) and 10 mg thrice (group 3) daily. All patients were also prescribed propranolol 20 mg thrice daily for the first 4 weeks. Blood was taken for total T3, T4, TSH, blood counts and liver enzymes determinations at the beginning and at 6 weeks of treatment. Only 48 (68.6%) patients were included in the analysis, as the rest defaulted follow-up (20.0%) or blood samples were not available at review (11.4%). Of the 48 patients, 17 were in group 1, 16 in group 2 and 15 in group 3.

Following 6 weeks of treatment, there was no significant difference in the mean serum levels of total T3 and T4 between the 3 groups. However, there was a significant decrease in the mean serum levels of total T3 and T4 as compared to the start of the treatment.

Four patients (23.5%) in group 1, 4 patients (25%) in group 2 and 3 patients (20%) in group 3 were still thyrotoxic at 6 weeks of treatment, whilst 10 patients (58.8%) in group 1, 6 patients (37.5%) in group 2 and 3 (20%) in group 3 were biochemically hypothyroid. There was no significant difference in total white cell count, serum alanine aminotransferase (ALT) and aspartate transaminase (AST) values between the 3 groups.

In conclusion, carbimazole given in once or twice daily doses was as effective as when given in thrice daily doses in the treatment of thyrotoxicosis, with no adverse effect on white cell count and liver enzymes.

Key words: Carbimazole, thyrotoxicosis.

Introduction

Carbimazole is widely used in the medical treatment of hyperthyroidism and is regarded as the drug of choice^{1,2}. Its short half-life, however, has led to most people using it on a divided daily dose every 6 to 8 hours^{3,4}. Such a schedule is inconvenient for most patients and some would not be able to follow the dosing instructions strictly. However, studies of Pittman *et al*⁵ have shown selective binding of methimazole into thyroid tissue and the data of Wartofsky and Ingbar⁶ indicate a duration of action of a single dose of 30 mg methimazole of 24 to 36 hours, despite the shorter biological half-life, when assessed on blood levels. It is therefore possible to use methimazole at a less-frequent interval daily. The purpose of this study was to assess the effect of different regimes of carbimazole dosing intervals on thyroid function in patients with hyperthyroidism.

Subjects and Methods

Seventy patients with untreated hyperthyroidism attending the Endocrine Clinic of Hospital Universiti Sains Malaysia, Kubang Kerian, Kelantan, were enrolled in this study. These patients were confirmed to have hyperthyroidism both clinically and biochemically. The patients were randomly allocated into 3 groups. Patients in group 1 were given carbimazole 30 mg as a once daily dose, patients in group 2 were given carbimazole 15 mg twice daily and patients in group 3, 10 mg thrice daily — all for a duration of 6 weeks. In addition, all patients were also prescribed propranolol 20 mg thrice daily for a duration of 4 weeks, to control the thyrotoxic symptoms. Patients were re-examined at the end of 6 weeks and all investigations were repeated (except for thyroid ultrasound).

Investigations

Thyroid ultrasound

All ultrasound was done by one examiner (M.K. Zahary) and thyroid volume was estimated using a formula:

$$\text{volume} = \pi / 6 \times \text{length} \times \text{width} \times \text{depth}^2.$$

Full blood count

A full peripheral blood count was done using a Coulter counter S880 (USA):

Serum T3, T4 and TSH

Measurement of serum total triiodothyronine (T3), total thyroxine (T4) and thyrotropin (TSH) was done by radioimmunoassay using commercial kits (Abbott Laboratories, USA). The normal range for serum total T3, total T4 and TSH in our laboratory were 1.5-3.5 nmol/L, 66-166 nmol/L and less than 7 mIU/L respectively. For serum total T3 assay, the mean (range) intra-assay CV was 7.3% (6.2%-8.9%), the mean (range) inter-assay CV was 3.0% (2.0%-4.4%) and the sensitivity was 0.4 nmol/L. For serum total T4, the mean (range) intra-assay CV was 3.2% (2.5%-3.5%) and the sensitivity was 3 nmol/L. For serum TSH, the mean (range) intra-assay CV was 2.3% (2.0%-2.8%), the mean (range) inter-assay CV was 4.4% (3.7%-5.8%) and the sensitivity was 0.3 mIU/L.

Serum aspartate transaminase (AST), alanine transferase (ALT) and alkaline phosphatase (ALP)

Assays were done by spectrophotometric methods using reagents from Boehringer Mannheim, Germany.

Statistical Analysis

Wilcoxon signed rank test was used to compare between before and after treatment for each group; Mann Whitney U test was used to compare between different groups and Chi square test was used to compare group numbers. Analysis was done using Microstat statistical programme.

Results

Of the 70 patients, 48 (68.6%) completed the study. One patient was excluded because of development of skin rash following the start of carbimazole. The other 22 patients were excluded either because they defaulted follow-up (14 patients) or repeat investigations were not performed (8 patients). Of the 48 patients that completed the study, 17 patients were in group 1 (10 females and 7 males), 16 patients were in group 2 (10 females and 6 males) and 15 patients were in group 3 (13 females and 2 males). The mean (\pm SD) age of patients, mean (\pm SD) thyroid volume, mean (\pm SD) serum total T3, total T4 and TSH levels before treatment are shown in Table I. There was no significant difference in the means between the 3 groups except for serum total T3 level, which was higher in group 1 than in group 2 ($p < 0.02$) and for thyroid volume which was larger in group 2 than group 1 ($p < 0.02$). Mean (\pm SD) serum total T3, total T4 and TSH levels after 6 weeks treatment are shown in Table II. There was no significant difference in the means between the 3 groups. For all 3 groups, there was a significant decrease in the means of total T3 and total T4 levels as compared to the values at start of treatment. There was no significant difference in the change in the serum levels of total T3, total T4 and TSH before and after treatment between the 3 groups, as shown in Table III. There was no significant difference in the serum AST, ALT, ALP levels and white blood cell and platelet counts after 6 weeks of treatment between the 3 groups. The clinical and biochemical thyroid status of patients in the 3 groups at the end of 6 weeks treatment is shown in Table IV. Patients were deemed to be still thyrotoxic if they had symptoms and signs of thyrotoxicosis and the serum total T4 was greater than 166 nmol/L, and hypothyroid if they had symptoms and signs of hypothyroidism and the serum total T4 level was less than 66 nmol/L. Serum TSH level was not used in the hypothyroid criteria because of the known lag in the recovery of TSH response following treatment of hyperthyroidism¹⁵. There was a significant difference between group 1 and group 3 ($p < 0.05$), with more patients being hypothyroid in group 1 after 6 weeks of treatment.

Table I
Age, serum total T3, total T4 and TSH levels
and thyroid volume of patients before treatment

	Group 1 (mean \pm SD)	Group 2 (mean \pm SD)	Group 3 (mean \pm SD)
Age (years)	33.9 \pm 2.8	39.6 \pm 2.7	39.1 \pm 3.3
T3 (nmol/L)	7.1 \pm 0.7*	4.6 \pm 0.5*	5.8 \pm 0.6
T4 (nmol/L)	238 \pm 16	220 \pm 15	237 \pm 15
TSH (mIU/L)	1.1 \pm 0.1	1.0 \pm 0.1	1.4 \pm 0.2
Thyroid volume (ml)	18.7 \pm 4.2 [†]	35.6 \pm 7.2 [†]	22.3 \pm 5.1

* $p < 0.02$, [†] $p < 0.02$

Table II
Serum total T3, total T4 and TSH levels of patients before treatment

	Group 1 (mean \pm SD)	Group 2 (mean \pm SD)	Group 3 (mean \pm SD)
T3 (nmol/L)	2.6 \pm 0.4	2.2 \pm 0.3	2.0 \pm 0.3
T4 (nmol/L)	91 \pm 22	97 \pm 17	101 \pm 15
TSH (mIU/L)	6.5 \pm 3.1	2.4 \pm 1.1	2.3 \pm 1.1

Table III
Change in serum total T3, T4 and TSH levels after treatment

	Group 1 mean (range)	Group 2 mean (range)	Group 3 mean (range)
T3 (nmol/L)	-3.8 (-9.0 to +0.5)	-2.7 (-5.1 to +0.5)	-3.6 (-9.4 to -0.9)
T4 (nmol/L)	-147 (-344 to +5.0)	-123 (-263 to -23)	-126 (-269 to +6.0)
TSH (mIU/L)	+5.4 (-0.8 to +48.9)	+1.45 (-0.7 to +17.2)	+0.9 (-1.6 to +14.9)

Table IV
Thyroid status of patients at 6 weeks of treatment

	Euthyroid	Toxic	Hypothyroid
Group 1	3 (17.7%)	4 (23.5%)	10 (58.8%)*
Group 2	6 (37.5%)	4 (25.0%)	6 (37.5%)
Group 3	9 (60.0%)	3 (20.0%)	3 (20.0%)*

* $p < 0.05$

Discussion

This study showed that carbimazole was effective in controlling hyperthyroidism in the majority of patients (77.1%) by 6 weeks of treatment. Though there was no significant difference in the mean levels of serum total T3 and total T4 between the 3 groups after treatment, there was a significantly higher number of patients hypothyroid in group 1 than in group 3, suggesting that perhaps taking carbimazole 30 mg once daily was more potent than taking it 10 mg 3 times daily, or drug compliance was better in the group taking once daily than in the group taking thrice daily doses. The duration of action of antithyroid drugs did not appear to be correlated with plasma levels but appeared to be correlated with the size of the dose administered⁸ and the intrathyroidal concentration of the drug^{9,10}. Greer *et al*¹¹, in his study using daily doses of propylthiouracil or methimazole, claimed control in 29 out of 31 cases of hyperthyroidism though no laboratory data were included to support this claim. Kammeret *et al*¹² and Wise *et al*¹³ also reported on the successful use of daily doses of propylthiouracil in the former and carbimazole in the latter in the maintenance therapy of hyperthyroid patients after the conventional divided daily doses of the antithyroid drugs in the initial phase. Barnes *et al*¹⁴ also reported on the use of single daily dose methimazole with an overall 68% responders and suggested that those patients who had a high perchlorate discharge were more likely to respond. Macfarlane *et al*¹⁵, in their study using 30 mg of carbimazole as a single daily dose, achieved euthyroid state in two-thirds of their hyperthyroid patients after 9 weeks of treatment. However, no comparison was made with the conventional thrice daily dosing of carbimazole and no mention was made of hypothyroidism in their patients.

Except for 1 patient on the once daily regime who developed skin rash, there was no adverse effect noted in this study. There was no significant difference in the serum liver enzyme levels, white cell and platelet counts between the 3 groups after treatment.

In conclusion, carbimazole is also effective given as a single or twice daily dose in the treatment of hyperthyroidism. Perhaps a lower dose (i.e., less than 30 mg daily for 6 weeks) or a shorter duration of treatment (i.e., 30 mg daily for less than 6 weeks) should be used in the once daily than in the 3 times daily regime, in view of the higher incidence of hypothyroidism at 6 weeks of therapy.

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