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Do higher doses of carbimazole improve remission in Graves' disease?

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Summary

The aim of this study was to determine whether a course of carbimazole therapy in higher than normal doses could improve remission rates in Graves' disease, 77 patients were randomly allocated to one of two treatment groups. Group 1 ($n=33$) received a 12-month course of 60 mg/day carbimazole. Group 2 ($n=44$) received 45 mg/day for the first month, 30 mg/day for the second month, and 20 mg/day for the remaining 10 months. All patients were started on T3 between 2 and 4 months after commencing therapy, to maintain euthyroidism. After carbimazole/T3 therapy was withdrawn, patients were followed for either 12 months or until they relapsed. A total of 14 patients (five Group 1, nine Group 2) were withdrawn from the study. There was no significant difference in mean thyroid hormone levels between the two treatment groups during treatment. TT4 concentrations fell significantly faster during the first 4 weeks of treatment in Group 1 patients. Of the 63 patients who completed the study, 30 relapsed and 33 remained in remission. Of those who relapsed, 10 (33%) were from Group 1 and 20 (67%) from Group 2. Of those in remission, 18 (54%) were from Group 1 and 15 (45%) from Group 2. High doses of carbimazole were associated with few adverse side-effects and an improved remission rate.

Introduction

The antithyroid drugs carbimazole, methimazole its active metabolite, and propylthiouracil (PTU) are the first line of treatment for many thyrotoxic patients.[1] Despite the widespread use of these thionamide drugs, approximately 50% will relapse within 12 months of their therapy being withdrawn.[2] This figure has changed little since the drugs were first introduced over 40 years ago. In addition to this unacceptably high relapse rate, there is little general agreement on how the drugs are used, with wide variation between treatment centres on the length of the treatment period, the dosage, and whether or not thyroxine and triiodothyronine should be given concurrently. Despite these different treatment regimes, remission rates remain at about 50% in almost all centres.[3] Recent studies have suggested that higher doses of antithyroid drugs may help improve remission rates, although the patients in these studies did not receive the high dose for a prolonged period.[4,5] In addition, there have also been reports of dose-dependent toxicity associated with the administration of thionamide drugs[6] which may limit the value of the higher dose regimes. The role of either thyroxine or triiodothyronine in improving remission rates has been the subject of several recent studies. Hashizume *et al.*[7] found that administration of thyroxine after the hyperthyroidism was controlled with methimazole significantly improved remission rates. The problem, however, is that the patients were required to be on therapy for a further

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3 years after the hyperthyroidism was controlled. In a more recent study[8] where the thyroxine was not given for such a long period, the recurrence rates were not as good.

The aim of this study was to compare the effects of a 12-month course of a high dose of antithyroid drugs with a more conventional treatment regime, in terms of how quickly control was achieved and how many patients were in remission at 12 months after therapy was withdrawn. In addition, the problem of side-effects associated with the higher dose was considered.

Methods

We enrolled 77 patients into the study. Graves' disease was confirmed on the basis of clinical findings, a thyroid scan and elevated thyroid hormone levels (total T3, total T4 and TSH). All were positive for thyrotrophin receptor antibodies (TRAb) at presentation. None of the patients had previously received treatment for Graves' disease. The patients were randomly allocated to one of two treatment regimes. Group 1 ($n=33$) received a 12-month course of 60 mg/day carbimazole. T3 was added as required to keep the patients euthyroid and in most cases this was after 2 months treatment (mean 2.4 ± 0.9 months). Group 2 ($n=44$) received 45 mg/day carbimazole for the first month, 30 mg/day for the second month, and 20 mg/day for the remaining 10 months. Again, T3 was added as required to keep the patient euthyroid and generally this was after about 4 months (mean 4.5 ± 1.2 months).

All patients were followed for 12 months after therapy was withdrawn. During the 12-month treatment period, 14 patients withdrew. Five were from Group 1, of whom three suffered an adverse reaction to carbimazole (skin rash), one was lost to follow-up, and one was given ^{131}I therapy (at patient's request). Of the nine withdrawals from Group 2, six had an adverse reaction (skin rash), two were lost to follow-up, and one was given ^{131}I therapy (at patient's request). A total of 63 patients completed the study; 28 from Group 1 and 35 from Group 2.

The patients were sampled at presentation, at 1, 2, 4, 6, 8, 10 and 12 months after therapy began, and either at 1, 3, 5, 7, 9 and 12 months after therapy was withdrawn or until the patients thyrotoxicosis relapsed. On all occasions, thyroid hormone levels and TRAb levels were measured.

Measurements

Serum total thyroid hormone concentrations TT3 and TT4 were measured by in-house radioimmunoassay and TSH concentrations by an immunofluorometric method (Delfia Systems, Pharmacia). Normal ranges for TT3, TT4 and TSH were 0.8–2.2 nmol/l, 55–144 nmol/l, and 0.005–5 mU/l, respectively. TRAb levels were measured using a radioreceptor assay purchased from RSR. Normal level was <10 units/ml.

Statistics

Results are expressed as means $\pm$ SD. Data were compared using the Mann-Whitney test. A statistical analysis tested whether high-dose therapy had a significant effect on remission rates, using a comparison of two independent binomials.

Results

Prior to commencing therapy, TT3, TT4 and TRAb concentrations were elevated and TSH concentrations suppressed in all patients. There were no significant differences between groups at this time (Table 1). Once the patients commenced treatment, TT3, TT4 and TRAb concentrations decreased and TSH concentrations rose in all patients. By 2 months after the start of treatment, concentrations had decreased to euthyroid or hypothyroid levels in all patients. There were no significant differences in thyroid hormone levels between groups at this time. Whilst there was no significant difference in the rate at which TT3, TSH and TRAb concentrations normalized, TT4 concentrations decreased significantly faster in Group 1 patients (Figure 1).

During treatment, TT3 concentrations fell sharply during the first 2 months of treatment as the thyrotoxicosis came under control. Levels rose in Group 1 patients after 2 months treatment and after 4 months in Group 2 patients. The rise is explained by the patients commencing T3 replacement therapy. At 12 months after the start of treatment, mean T4 levels for both groups were <65 nmol/l. The decrease was initially due to the thyrotoxicosis becoming controlled, and thereafter was the result of the T3 replacement therapy. Mean TSH concentrations increased following the start of treatment. This increase was greater in Group 2 patients, as they did not commence T3 therapy until 4 months after the start of treatment. There were few time-points during the treatment period when there were any significant differences in thyroid hormone levels between the two treatment groups (Table 1).

Table 1 shows that TRAb concentrations decreased following carbimazole therapy, but by 12 months after the start of treatment, mean concentrations were

Table 1 Effect of therapy on hormone levels

Hormone	Group 1 Time on treatment (months) 0	1	2	4	6	8	10	12
T3	5.7±2.6	2.9±1.7	2.2±1.3	3.5±1.2	3.9±1.2	4.3±12.4	3.7±12	3.9±2
T4	232±55	99±49	66±52	30±34	34±40	49±68	52±59	47±66
TSH	0.19±0.1	0.7±1.5	4.4±10	2.1±4.7	6.9±18	1.5±2.7	1.0±2.7	2.2±4.4
TRAb	48±30	31±32	17±24	30±22	27±24	16±15	16±23	11±24
	Group 2 Time on treatment (months)							
	0	1	2	4	6	8	10	12
T3	4.8±1.8	2.7±1.3	2.1±1.0	2.1±0.9***	3.2±1.4*	3.6±1.7	3.8±1.2	3.4±1.4
T4	215±45	122±67	89±54	81±67**	68±59	58±53	47±57	60±55
TSH	0.19±0.1	0.5±1.0	8.5±17	13.4±25	7.4±19	1.4±2.5	0.6±1.0	1.2±2.1
TRAb	35±16	24±22	11±18	15±19*	29±50	20±21	9±22	22±21

Results are means±SD.
*$p<0.08$ vs. Group 1; **$p<0.002$ vs. Group 1; ***$p<0.009$ vs. Group 1.

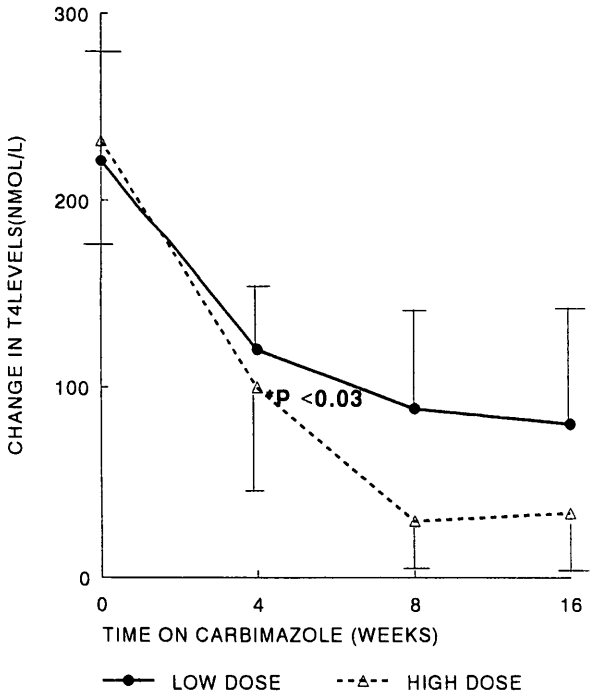

Figure 1. Changes in T4 levels following carbimazole therapy.

still above the upper limit of the reference range of 10 units for both groups. However, Table 2 shows mean TRAb levels at 0 and 12 months after the start of treatment in those patients who relapsed and those who remained in remission in Groups 1 and 2. Higher TRAb levels were found in those patients who relapsed, regardless of their treatment group.

In the 12 months following the withdrawal of therapy, 30 patients relapsed and 33 remained in remission. Of those who relapsed, 10 (33%) were from Group 1 and 20 (67%) were from Group 2. Of the 33 in remission, 18 (54%) were from Group 1 and 15 (45%) from Group 2. While patients in Group 1 appeared to have a better chance of remaining in remission, analysis of the data by a comparison of two independent binomials showed no significant difference between the groups.

Discussion

In this study, a higher dose of carbimazole therapy resulted in T4 concentrations decreasing towards normal more quickly than with a conventional dose. There was no significant difference in the rate of decrease of T3 or increase in TSH levels between the two groups. There were few significant differences in mean thyroid hormone concentrations between the two groups throughout the treatment period. The present study is one of many that has been conducted over the years. Comparisons between studies are difficult, as different groups use different treatment protocols, different doses and even different drugs. The earlier study of Romaldini et al.[4] where patients received high doses of methimazole (60±14.5 ng/day) or PTU (694±173 mg/day) for 10–30 months, found significant differences in T3, TSH and FT4 levels between the two treatment groups when changes in the above analytes were calculated at 3-monthly intervals over the treatment period. This treatment regime resulted in a 75% remission rate. While this remission rate is clearly

Table 2 Reductions in TRAb levels over the 12-month treatment period

Outcome	*n*	Treatment group	Time (months)		*p*
			0	12	
Relapse	10	1	57.5±25	22.5±20	<0.01
Relapse	20	2	36.2±12	24.1±17	<0.01
Remission	18	1	38.5±27	1.5±17	<0.001
Remission	15	2	30.4±19	5.7±4.3	<0.001

Data are means±SD.

greater than our own, this is no doubt due, at least in part, to the longer treatment period. Like the present study, they found the higher dose to be associated with few adverse reactions. This is in marked contrast to the earlier and much smaller study of Wiberg *et al.*[6] who found that 9/25 patients who had received 120 mg/day methimazole developed toxic reactions within 4 months. They concluded that the high incidence of toxicity negated the advantages gained by the more rapid control of the thyrotoxicosis. The reason why their rate of adverse reactions should be so much greater than our own is not clear. In 1993, Reinwien[5] compared the effects of 40 vs. 10 mg/day methimazole. The 40 mg dose was associated with a significant improvement in the rate at which patients became euthyroid ($p<0.01$), although there was no significant difference in the therapeutic index calculated for the first 12 weeks between the groups. However, the higher dose gave no significant improvement in remission rates and was associated with a high incidence of adverse reaction.

In our study, treatment was for 12 months and no attempt was made to consider the effects of length of treatment. Previous studies have considered treatment periods of between 6 months and 2 years, and from the results obtained it would appear that there is only a significant improvement in remission rates if the treatment period is increased to 2 years.[9] Treatment periods of between 6 and 12 months appear to give no significant difference in remission rates.[10,11] A recent study from Japan has concluded that the main protection against relapse is neither the duration of treatment or the dosage given but the use of levo T4, which the authors continued after the drug therapy was stopped.[7]

Controversy exists as to whether or not antithyroid drugs have an immunosuppressive effect. In agreement with previous studies by ourselves and others,[12,13] the significant fall in TRAb levels over the 12 month treatment period would support the view that carbimazole does have an immunosuppressive effect, although there was no significant difference in mean values between the two treatment groups. The decrease in TRAb concentrations over the 12-month treatment period was however significantly greater for the higher dose group (38±32 vs. 10±15, $p<0.003$). Reinwein *et al.*[5] found the 76% of patients who were positive for TRAb levels at the start of treatment fell to 30% after 12 months of 40 mg/day methimazole. This compared with 68% falling to 25% in the 10 mg/day group. The use of TRAb levels as indicators of patients likely to relapse has been the subject of many previous studies. Whilst the findings of these studies have differed, it appears that while TRAb levels may be of some value in prediction, this is not possible until 12 months after the start of treatment. In this study, the TRAb levels obtained at the end of 12 months treatment correctly predicted the final outcome in 80% of patients. A recent paper used meta-analysis to review the results in the literature on the effect of the presence or absence of TRAb at the end of treatment. They found the absence of TRAb was protective against relapse, but concluded that the present methods of assaying for TRAb do not allow sufficiently high prediction of relapse or remission for individual patients.[14]

In conclusion, in this study, a 12-month course of high-dose carbimazole therapy lead to improved remission rates. While statistical analysis showed no significant difference between the groups, this may be due to the numbers involved, and a larger study might well reveal a significant difference rather than a trend. The lack of adverse side-effects would suggest that it may be possible to increase the dose and/or treat for longer to increase remission rates still further. In view of the number of studies suggesting that increased remission rates are the result of increased treatment periods and/or increased dosage regimes, perhaps the various treatment centres should now consider using higher dosages as standard.

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