

SINGLE DAILY DOSE CARBIMAZOLE IN THE TREATMENT OF GRAVE'S DISEASE

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SYNOPSIS

The effectiveness of a single daily dose of carbimazole in the treatment of Grave's disease has been well documented but has not received wide clinical usage. Twenty-four patients with Grave's disease (nine of which had already been on treatment with the conventional thrice daily regime for an average duration of three months) were given a single daily dose of carbimazole to induce and maintain a remission. Only one patient failed to achieve a satisfactory remission. Once in remission, a single daily dose of carbimazole was effective in maintaining it. A distinct patient preference for the single daily dose regime was noted.

INTRODUCTION

The thiocarbamide group of antithyroid drugs like carbimazole and propylthiouracil are usually the first line of treatment in Grave's disease. It is probably the commonest form of treatment in Malaysia. Most textbooks (Goodman and Gilman, 1975; Conn, 1978; Krupp and Chatton, 1978) recommend that the drugs should be administered at 8 hourly intervals because of their relatively short plasma half-life.

Several reports, however, have suggested that the 8 hourly administration of carbimazole and propylthiouracil may be unnecessary. It is not the plasma concentration but the intrathyroidal concentration of the drug which is important in determining its duration of action (Marchant *et al*, 1971; Lazarus *et al*, 1975). The antithyroid drugs are selectively concentrated in the thyroid gland and if a sufficiently large dose has been given, they may continue to be active far longer than eight hours after ingestion and absorption (Marchant *et al*, 1971; Lazarus *et al*, 1975). Methimazole, given in a single 30 mg dose, has been shown to inhibit the organification of iodine for at least 24-36 hours (Wartofsky and Ingbar, 1971). If plasma half-life was the only criteria in determining the duration of action of these drugs, then propylthiouracil would have to be given far more frequently than recommended because its half-life is only 2½ hours!

Since the duration of treatment of Grave's disease at different centres would vary from six months to as long as two years, the use of a single daily dose regime would greatly simplify management and lighten the patient's burden. Greer *et al*, (1965) and Kammer and Srinivasan (1969) have used a single daily dose of a thiocarbamide to treat their patients with Grave's disease and have reported fair results.

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I report here a trial to test the efficacy of a single daily dose of carbimazole in inducing and maintaining a remission in Grave's disease in the local population. (Carbimazole is converted to Methimazole in the body).

PATIENTS

All cases of Grave's disease seen by the author since December 1977 were considered for the trial. In the case of patients already on treatment with the thrice daily regime, it was decided not to include any cases who had been on treatment for more than 6 months. The one exception was a patient who had been on treatment for 7 months already and had threatened to default because of the inconvenience of the thrice daily regime. Several

patients defaulted after a follow-up period of less than three months and two patients developed allergy to carbimazole. They were excluded from the trial.

Finally, only 24 patients were considered suitable for this trial. They were divided into three groups:—

- (A) Newly diagnosed cases, not on treatment
- (B) Relapsed cases, not on treatment, and
- (C) Either new or relapsed cases who were already

on thrice daily carbimazole for a period varying from two weeks to seven months (the average duration was three months).

Their data are contained in the three accompanying tables.

**TABLE I
GROUP A**

Grade A	Race	Age (years)	Sex	Goitre Size (Grade)*	Period of follow-up (months)	Remarks
TYK	Chinese	28	F	2	5	Defaulted
HSG	Chinese	25	F	0	5	
YHL	Chinese	32	F	1	7	
LPL	Chinese	22	F	1	8	Pregnant
LML	Chinese	22	F	2	8	
WSY	Chinese	37	F	2	8	
LKC	Chinese	35	F	1	9	
LY	Chinese	35	F	2	11	
FKL	Chinese	32	F	2	16	

*This refers to the system of grading thyroid gland size at the Endocrine clinic of the University Hospital.

- Grade 0 Not palpable to just palpable
- Grade 1 Just visible, mildly enlarged
- Grade 2 Moderately enlarged
- Grade 3 Very large
- Grade 4 Monstrous goitres

**TABLE II
GROUP B**

Group B	Race	Age (years)	Sex	Goitre Size (Grade)*	Period of follow-up (months)	Remarks
CFY	Chinese	27	F	1	3	Pregnant
NGH	Chinese	21	F	1	3	
SM	Chinese	30	F	2	6	
WKL	Chinese	19	F	3	8	
NWH	Chinese	26	M	2	8	
YYL	Chinese	27	F	2	10	Treatment failure

*This refers to the system of grading thyroid gland size at the Endocrine Clinic of the University Hospital.

- Grade 0 Not palpable to just palpable
- Grade 1 Just visible, mildly enlarged
- Grade 2 Moderately enlarged
- Grade 3 Very large
- Grade 4 Monstrous goitres

TABLE III
GROUP C

Grade C	Race	Age (years)	Sex	On thrice daily regime (months)	Follow-up on single dose regime (months)	Goitre Size (Grade)*	Remarks
TKY	Chinese	23	F	7	8	1	New case
WAS	Chinese	36	F	2	8	1	New case, defaulted
NYK	Chinese	23	F	5	10	1	New case, Pregnant, delivered uneventfully
SH	Malay	27	F	3	13	2	Relapsed case
TF	Malay	38	F	4	13	1	New case
YLS	Chinese	30	M	1	14	2	New case
LSF	Chinese	22	F	1	15	2	New case. Still toxic when single dose regime started.
LSM	Chinese	25	F	½	15	2	New case
TSB	Chinese	16	F	2	15	2	New case

*This refers to the system of grading thyroid gland size at the Endocrine clinic of the University Hospital.

Grade 0 Not palpable to just palpable

Grade 1 Just visible, mildly enlarged

Grade 2 Moderately enlarged

Grade 3 Very large

Grade 4 Monstrous goitres

METHOD

Carbimazole in a single daily dose of 30 mg was prescribed to all toxic patients. As they became euthyroid, the dose was gradually reduced to a maintenance dose of 15 mg daily. Patients who were already on the thrice daily regime were started at a lower single daily dosage if they were euthyroid or mildly toxic only.

Initial follow-up was at two to four weekly intervals depending on the degree of toxicity when first seen. No attempt was made to assess the duration of treatment required before patients became euthyroid as this would entail a weekly follow up at least. At each visit, the patients were assessed clinically, and in addition, they were also asked the following questions:—

- (1) Do you have an exacerbation of symptoms at any particular time of the day?
- (2) Do you feel worse off just before the next dose is due? and
- (3) Do you prefer the single daily dose or thrice daily treatment regime? (This last question was only directed at the 15 patients who had been on the thrice daily regime before).

Presently, our unit policy is to treat all patients for a period of 18 months before discontinuing treatment.

RESULTS

Most patients were euthyroid by the first or second visit after the initiation of therapy. If they were not euthyroid yet, they were at least clearly improving, with the excep-

tion of one patient, YYL from Group B. The general impression was that it did not take longer for patients on the single daily dose regime to become euthyroid. Once euthyroid they were easily maintained on a single daily 15 mg dose of Carbimazole. The presence of a large gland or severe symptoms did not appear to make the control of the disease any more difficult.

Only one patient (YYL, Group B) complained of an exacerbation of symptoms before the next dose of carbimazole was due. Eight weeks after beginning treatment, at her second follow-up, she complained that she had not improved much and her weight had continued to fall. On examination then, she was mildly agitated. Her pulse rate was 84 per minute and her palms were cool and dry. However, finger tremors and a thyroid bruit were still present. She was then put on carbimazole 15 mg thrice daily for four weeks and at the end of this period she was euthyroid and had gained half a kilogram in weight. She was put back on carbimazole at a single daily dose of 30 mg and has been on the single dose regime since with no further problems.

With this exception, the remaining 14 patients who had been on the thrice daily regime before clearly stated that they preferred the new regime for its simplicity and convenience.

DISCUSSION

The treatment of Grave's disease with antithyroid drugs may be conveniently divided into two phases. Firstly, the induction phase from the onset of therapy till the patient becomes euthyroid, and secondly, the maintenance

phase. Of the 24 patients reported, only YYL can be considered a treatment failure during the induction phase. Since she was one of the earlier cases encountered in this trial (before much experience had been gained on the efficacy of the single dose regime in our local population), I felt compelled to put her on our standard regime of carbimazole 15 mg thrice daily till she became euthyroid. In retrospect, however, perhaps the higher total daily dosage was the critical factor leading to her improvement rather than the fact that it was given thrice daily. If I were to encounter such a problem again, I would probably increase the single daily dosage of carbimazole to 40 mg.

As far as the maintenance phase is concerned, there is little doubt that a single 15 mg dose of carbimazole is as effective as the conventional dose of 5 mg thrice daily. An even lower single dose of 10 mg was considered but it was decided not to use it for the time being. At the time of writing, the period of follow-up ranged from three months to sixteen months. Long term follow-up, however, is not critical in evaluating the efficacy of the single daily dose regime. There are now reports that a lasting remission may occur in a fair proportion of patients after only a short period of treatment. Greer *et al*, (1977) reported that their patients who were treated for only three to four and a half months (till they were euthyroid or shortly after that), had as good a remission as those treated for a year or more. Therefore, if a patient has already gone into remission with the initial phase of treatment, further treatment, whether with the single dose or thrice daily regime, or no treatment at all, will give the same result.

It is significant that of the 15 patients who had already been on treatment with the thrice daily regime (either during a previous course of treatment or at the beginning of the present course), 14 clearly preferred the single dose regime. Being in a position to compare their own progress and well-being under the two regimes makes their opinion all the more meaningful.

CONCLUSION

This study suggests that a single daily dose of carbimazole is effective in the treatment of our local patients with Grave's disease. An initial daily dose of 30 mg is recommended, and if difficulty is encountered in rendering a patient euthyroid, a higher dose is suggested. Long term maintenance on carbimazole 15 mg daily was adequate for all patients.

This regime greatly simplifies the management of a disease which usually requires prolonged treatment and may lead to improve patient compliance.

ACKNOWLEDGEMENT

I wish to thank Associate Professor A. Ngan for her helpful advice.

ADDENDUM

Since the above article was written, further experience has been gained in the use of the single daily dose regime. It is practical to start treatment with Carbimazole in a single daily dose of 30 mg and then reduce it by 10 mg at a time to a maintenance dose of 10 mg daily after eight to twelve weeks.

If there is poor response to 30 mg of Carbimazole daily after a reasonable period (4 — 6 weeks), then increasing the dose to 45 mg daily will render the patient euthyroid within 2 — 3 weeks.

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