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Comparison of the Efficacy and Safety of Antithyroid Drugs

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ABSTRACT

We performed a retrospective cohort analysis of 214 patients with untreated Graves' disease. Three groups of patients were studied : those who had started treatment with methimazole (MMI) at a dosage of 15 mg/day (MMI15 group, $n=77$), those who had been treated with MMI at 30 mg/day (MMI30 group ; $n=72$), and those who had been treated with propylthiouracil (PTU) at a dosage of 300 mg/day (PTU300 group ; $n=65$). The final analysis included 67 patients of the MMI15 group, 47 patients of the MMI30 group, and 42 patients of the PTU300 group. The patients were observed from primary diagnosis until a euthyroid state was achieved. A variety of clinical factors were evaluated. Survival analysis and the log-rank test showed significant differences in therapeutic efficacy between the MMI15 group and PTU300 group and between the MMI30 group and the PTU300 group when the serum level of free thyroxine (FT_4) was high. Analysis with Cox proportional hazards regression models showed that treatment efficacy was not effected by FT_4 levels, serum levels of thyroid-stimulating hormone receptor antibody (TRAb), or the estimated thyroid gland weight. Multivariate analysis adjusted for other clinical factors showed significant differences in therapeutic efficacy between the MMI30 group and the PTU300 group. Only serum FT_4 and TRAb levels affected that difference. The rate of adverse effects was less in MMI15 than in MMI30 or PTU300. In conclusion, MMI at a dosage of 15 mg/day is as effective as MMI at 30 mg/day or PTU at 300 mg/day, and MMI at 15 mg/day is safer than MMI at 30 mg/day or PTU at 300 mg/day. (Jikeikai Med J 2006 ; 53 : 93-9)

Key words : hyperthyroidism, Graves' disease, methimazole, propylthiouracil

INTRODUCTION

Antithyroid drugs have been used to treat hyperthyroidism due to Graves' disease for many years. Although methimazole (MMI) has been used since 1956 and propylthiouracil (PTU) since 1966, the optimal dosage schedules remain controversial in Japan. Several investigators have reported the effectiveness of MMI administered as a single standard daily dose (30 or 40 mg/1×)[1-4] or as low daily dose (10 mg/1×)[5,6] for the initial treatment of Graves' disease. Randomized trials have compared a low daily dose (10 or 15 mg/day) with a standard dose (30 or 40 mg/day) of MMI[7-11]. These studies found no significant differences in efficacy between a low daily dose and a standard dose of MMI. However, whether a low daily dose of MMI is as effective as the standard dose when serum thyroid hormone levels are high is uncertain. Furthermore, other factors have not been examined. Trials comparing MMI and PTU[12-14] have shown that MMI is more effective than PTU.

We investigated whether there were any differ-

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ences in the effectiveness of a low daily dosage of MMI (15 mg/day), a standard dosage of MMI (30 mg/day), and PTU (300 mg/day), and whether the response to treatment is influenced by sex, age, weight, smoking, alcohol, pulse rate, usage of β-blockers, thyrotoxic symptoms, the serum level of free thyroxine (FT_4), the serum level of thyroid-stimulating hormone (TSH) receptor antibody (TRAb), or estimated thyroid gland weight.

Because adverse effects are reportedly less frequent with a low daily dose than with a standard dose of MMI[15,16], we also investigated the rate of adverse effects in each group.

Patients and Methods

Patients

Two hundred fourteen patients with untreated hyperthyroidism due to Graves' disease who had visited Ito Hospital, Tokyo, from August 1, 2003, through April 30, 2004, were studied retrospectively.

Graves' disease was diagnosed on the basis of elevated serum levels of thyroid hormone (serum $FT_4 > 1.60$ ng/dl), suppressed serum levels of TSH (serum TSH < 0.20 μU/ml), and positive TRAb levels (TRAb $> 15\%$). Exclusion criteria included complications of thyroid crisis, atrial fibrillation, heart failure, and pregnancy.

This study was approved by the ethical committee of the Jikei University School of Medicine.

Laboratory tests

Serum concentrations of FT_4 and TSH were measured with radioimmunoassay using commercially available kits (Elecsys FT_4, Elecsys TSH, Roche Diagnostics, Basel, Switzerland) or equilibrium dialysis when FT_4 levels were greater than 7.77 ng/dl. The normal range in our laboratory for FT_4 is 0.80 to 1.60 ng/dl, and that for TSH is 0.20 to 4.50 μU/ml. Levels of TRAb were measured with radioreceptor assay (TRAb CT [Cosmic], Cosmic Corporation, Tokyo, Japan). The weight of the thyroid gland was estimated with the Okubo method using the traced thyroid gland by palpation[17].

Study design and endpoints

Three groups of patients were studied: those who had begun treatment with MMI at a dose of 15 mg/day (MMI15 group), those who had received MMI at 30 mg/day (MMI30 group), and those who had received PTU at a dose of 300 mg/day (PTU300 group).

We investigated whether patients had become euthyroid in the following period and the time until the euthyroid state was achieved. The euthyroid state was defined as normalization of the serum TSH level. We also examined the rate of adverse effects in each group.

The patients in each treatment group were stratified into 2 subgroups according to the serum FT_4 level ($FT_4 \geqq 7.50$ ng/dl or $FT_4 < 7.50$ ng/dl) to examine the rate of achieving the euthyroid state and the time to achieve the euthyroid state in each group.

Statistical analysis

The rate of achieving the euthyroid state in each group was examined with the χ^2 test. The time to achieve the euthyroid state in each group was examined with the Kruskal-Wallis test in two subgroups stratified according to the serum FT_4 level. Survival analysis and the Log-rank test were performed to compare each group with the other groups. Cox proportional hazard regression models were used to examine the relation of the therapeutic dose of MMI with the serum FT_4 level, the estimated weight of the thyroid gland, and the serum TRAb level. Multivariate analysis was performed with Cox proportional hazard regression models adjusted for several variables. The variables include sex, age, weight, smoking, alcohol, pulse rate, use of a β-blocker, thyrotoxic symptoms, serum FT_4 level, estimated thyroid gland weight, and serum TRAb level.

The rate of adverse effects in each group was examined with the χ^2 test.

Multiple comparisons were performed at the 0.017 significance level. All analyses were performed according to the intention-to-treat principle.

Results

Patients profiles

Initially, 77 patients were in the MMI15 group, 72 in the MMI30 group, and 65 in the PTU300 group. However, 4 patients were excluded from the analyses owing to poor compliance, and 54 patients were excluded owing to adverse effects of antithyroid drugs. Therefore, included in the final analysis according to the intention-to-treat principle were 67 of 77 patients in the MMI15 group, 47 of 72 patients in the MMI30 group, and 42 of 65 patients in the PTU300 group (Table 1).

Serum FT_4 levels, the estimated weight of the thyroid gland, and serum TRAb levels did not differ significantly within the three groups stratified into 2 subgroups in each treatment group on the basis of FT_4 levels (Kruskal-Wallis test).

Efficacy end points

The median follow-up period was 174 days (range, 16-462 days).

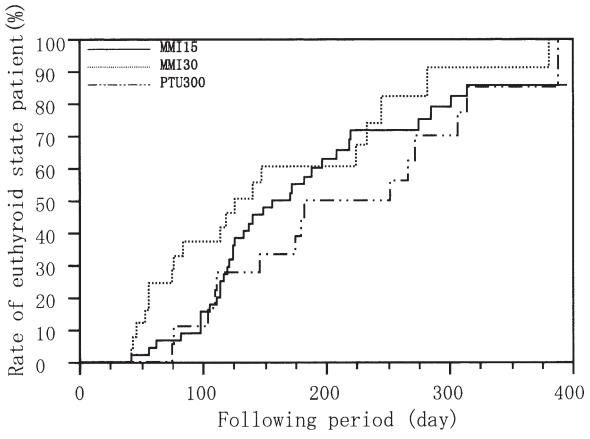
In the subgroup of patients in whom FT_4 levels were less than 7.50 ng/dl, the euthyroid state was achieved in 34 of 47 patients in the MMI15 group, 19 of 25 patients in the MMI30 group, and 15 of 19 patients in the PTU300 group. The percentages of patients achieving the euthyroid state did not differ among these groups (χ^2 0.34 $p=0.843$). The time to achieve the euthyroid state also did not differ significantly (χ^2 4.74 $p=0.094$). In the subgroup of patients with serum FT_4 levels of 7.50 ng/dl or greater, the euthyroid state was achieved in 12 of 20 patients in the MMI15 group, 19 of 22 patients in the MMI30 group, and 7 of 23 patients in the PTU300 group. The percentages of patients achieving the euthyroid state differed among the MMI15 group, the MMI30 group and the PTU300 group using the χ^2 test (χ^2 14.51 $p=0.0007$). There were significant differences only between MMI30 group and PTU300 group (χ^2 14.42 $p=0.0001$). The time to achieve the euthyroid state did not differ significantly with the Kruskal-Wallis test (χ^2 0.81 $p=0.666$).

In patients with serum FT_4 levels less than 7.50 ng/dl, therapeutic efficacy did not differ among the 3 treatment groups (χ^2 2.64 $p=0.267$) (Fig. 1). However, in patients with FT_4 levels of 7.50 ng/dl or greater, therapeutic efficacy differed significantly among the MMI15 group, the MMI30 group, and the PTU300 group (χ^2 9.56 $p=0.008$). The therapeutic

Table 1. Characteristics of patients in final analysis

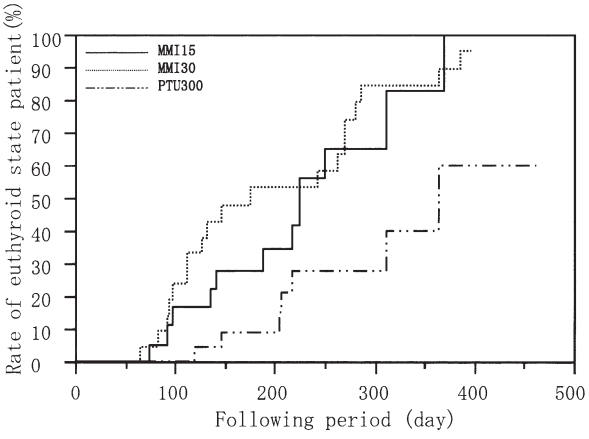
	MMI15 mg		MMI30 mg		PTU300 mg		*p*-value	
FT_4 (ng/dl)	<7.50	≧7.50	<7.50	≧7.50	<7.50	≧7.50	<7.50	≧7.50
Number of patients	47	20	25	22	19	23		
Age (yr ; median, range)	40, 17-61	37.5, 16-66	47, 17-60	31.5, 21-59	41, 19-58	33, 22-53		
Females/males	35/12	16/4	20/5	15/7	18/1	21/2		
Height (cm ; median, range)	158.5, 144.0-190.3	158.8, 146.8-167.6	156.6, 147.2-176.0	163.6, 148.0-178.4	158.8, 144.3-168.0	157.5, 152.2-180.0		
Weight (kg ; median, range)	50.0, 41.2-85.0	49.0, 36.9-60.7	52.7, 35.4-78.0	53.2, 46.2-71.8	50.0, 37.8-64.9	51.0, 40.0-71.2		
Smoking +/−	15/31	11/9	8/16	15/7	3/16	10/13		
Alcohol +/−	31/15	14/6	13/11	10/12	6/13	14/9		
Pulse rate (median, range)	98, 64-138	106.5, 78-150	104, 71-131	105.5, 87-130	98, 58-132	113, 78-135		
β-blocker +/−	15/32	15/5	20/5	16/6	5/14	15/8		
Thyrotoxic symptoms +/−	30/17	17/3	19/6	17/5	16/3	11/12		
FT_4 (ng/dl ; median, range)	4.62, 2.25-7.27	12.70, 7.50-39.30	5.39, 2.21-7.28	11.55, 7.66-29.60	4.08, 1.83-6.75	16.80, 7.65-46.90	0.17	0.14
Estimated weight of thyroid gland (g ; median, range)	31.5, 3.0-81.0	54.0, 18.8-109.4	34.1, 3.8-63.3	58.5, 7.3-185.6	28.6, 5.0-59.6	50.7, 25.3-96.8	0.99	0.55
TRAb (% ; median, range)	62.0, 12.1-93.0	70.0, 33.8-90.1	68.0, 21.4-96.2	73.3, 49.6-93.3	71.6, 29.0-86.3	66.1, 47.1-95.1	0.55	0.36

Characteristics of patients in final analysis.
p-value means serum FT_4 levels, estimated weight of thyroid gland and serum TRAb levels of the patients were not different significantly within three groups stratified into 2 subgroups (Kruskal-Wallis test).



λ^2 2.64 $p=0.267$

Fig. 1. Survival analysis and log-rank test when serum FT_4 level is <7.50 ng/dl. There were no significant differences among the three groups.



λ^2 9.56 $p=0.008$
MMI15 vs MMI30 : λ^2 0.38 $p=0.532$
MMI15 vs PTU300 : λ^2 5.55 $p=0.018$
MMI30 vs PTU300 : λ^2 9.75 $p=0.002$

Fig. 2. Survival analysis and log-rank test when serum FT_4 level is $\geqq 7.50$ ng/dl. There was a significantly better response in the MMI30 group than in the PTU300 group.

Table 2. Interaction effect of therapeutic dose

	Hazard ratio	95% Confidence interval		Likelihood ratio
		lower	upper	p-value
Serum FT_4 level	1.00	0.93	1.09	0.82
Estimated weight of thyroid gland	1.00	0.98	1.02	0.60
Serum TRAb level	1.00	0.97	1.02	0.99

Interaction effect of therapeutic dose of MMI and serum FT_4 level, estimated weight of thyroid gland and serum TRAb level. For all variables, $p \geqq 0.05$. There were no interaction effects of therapeutic dose of MMI and these variables.

efficacy did not differ between the MMI15 group and the MMI30 group (χ^2 0.38 $p=0.532$) but was significantly more effective in the MMI15 group than in the PTU300 group (χ^2 5.55 $p=0.018$) and in the MMI30 group than in the PTU300 group (χ^2 9.75 $p=0.002$) (Fig. 2).

There were no significant differences found in the analysis that examined any interaction effect between treatment and serum FT_4 levels, estimated weight of thyroid gland, and serum TRAb levels in either the MMI15 group or the MMI30 group (Table 2). This means serum FT_4 levels, estimated weight of thyroid gland, and serum TRAb levels had no influence on the therapeutic dose of MMI. Multivariate analysis revealed no significant differences in therapeutic efficacy between MMI15 and MMI30 or between MMI15 and PTU300 but did show a significant difference in therapeutic efficacy between MMI30 and PTU300 (Table 3). The p-value in the likelihood ratio of all variables other than serum FT_4 levels and serum TRAb levels was $\geqq 0.05$.

Safety endpoints

We analyzed 210 patients, and 4 patients were excluded owing to poor compliance. The percentage of patients with an adverse effect of any type was significantly lower in the MMI15 group (11.8%, 9 of 76 patients) than in the MMI30 group (32.9%, 23 of 70 patients, χ^2 9.40 $p=0.002$) or the PTU300 group (34.4%, 22 of 64 patients, χ^2 10.23 $p=0.001$). The rate of drug allergy was significantly higher in the MMI30 group (25.7%, 18 of 70 patients) than in the MMI15

Table 3. Multivariate analysis

	Hazard ratio	95% Confidence interval		Likelihood ratio	
		lower	upper	p-value	
MMI30	1.40	1.05	1.89	0.02	*
MMI15	1.25	0.95	1.66	0.10	
PTU300	1				
MMI30	1.12	0.86	1.45	0.39	**
MMI15	1				
Female sex	1.11	0.82	1.56	0.47	***
Age	1.00	0.98	1.02	0.43	
Weight	1.02	0.99	1.05	0.17	
Smoking	0.92	0.73	1.15	0.48	
Alcohol	0.96	0.78	1.19	0.74	
Pulse rate	1.01	0.99	1.02	0.09	
Usage of β-blocker	0.91	0.71	1.16	0.48	
Thyrotoxic symptoms	1.24	0.99	1.57	0.05	
Serum FT_4 level	0.95	0.91	0.99	0.01	
Estimated weight of thyroid gland	0.99	0.98	1.00	0.52	
Serum TRAb level	0.98	0.97	0.99	0.00	

*hazard ratio means therapeutic effect when that in PTU300 group is 1
**hazard ratio means therapeutic effect when that in MMI30 group is 1
***p-value shows whether these variables have influence on therapeutic effect

group (2.6%, 2 of 76 patients, χ^2 16.42 $p<0.0001$) or in the PTU300 group (7.8%, 5 of 64 patients, χ^2 7.54 $p=0.006$). The rate of liver damage was significantly higher in the PTU300 group (25.0%, 16 of 64 patients) than in the MMI15 group (7.9%, 6 of 76, χ^2 7.68 $p=0.006$) or the MMI30 group (5.7%, 4 of 70 patients, χ^2 9.79 $p=0.002$). Granulocytopenia was observed in 1 patient in the MMI30 group and in 1 patient in the PTU300 group. Alopecia was observed in 1 patient in the MMI15 group and in 1 patient in the MMI30 group. One patient in the PTU300 group had arthralgia during the course of treatment; the antineutrophil cytoplasmic antibody was also detected in this patient.

Discussion

Previous studies have found no significant difference in therapeutic efficacy between a low daily dose (15 mg/day) and a standard dose (30 mg/day) of MMI. We raised some questions in relation to these findings: "is a low daily dose of MMI as effective as the standard dose when serum thyroid hormone levels are very high?" and "how about serum TRAb levels, the size of the thyroid gland, and other clinical factors, such as symptoms and physical findings?" To answer these questions, we performed the analyses described above.

We found no significant differences in the therapeutic efficacy, irrespective of the high FT_4 levels ($\geqq$7.50 ng/dl), between the MMI15 group and the MMI30 group. These results show that 15 mg of MMI daily is as effective as 30 mg of MMI daily when the serum FT_4 level is high. We also found that the effectiveness of these doses was not affected by the serum FT_4 level, the estimated weight of the thyroid gland, or the serum TRAb level. It can be concluded that 15 mg of MMI daily is as effective as 30 mg daily when the serum FT_4 level is high, the thyroid gland is large, or the serum TRAb level is high. Multivariate analysis showed that the hazard ratio was not affected by sex, age, weight, smoking, alcohol, pulse rate, usage of β-blockers, thyrotoxic symptoms, or the estimated weight of the thyroid gland (Table 3).

These findings suggest that these clinical factors have no influence on the dosage schedule of MMI.

Some previous reports concerning treatment with a single daily dose (300 or 450 mg/1×)[18–20] or a low daily dose (150 mg/1×)[14] of PTU have suggested that PTU is not as effective as MMI, presumably because of intrathyroidal MMI accumulation[21]. It has also been reported that 30 mg of MMI given once daily is more effective in lowering serum T_3 levels than is PTU given as a 100 mg dose every 8 hours[12]. The present study also showed a significantly better response in the MMI30 group than in the PTU300 group. The likelihood ratio of the various treatments and the serum levels of FT_4 and TRAb is $p < 0.05$ (Table 3). This finding suggests that PTU is less effective when serum levels of FT_4 or TRAb are high.

In the present study, the rate of hepatic injury was significantly higher in the PTU300 group than in either of the MMI groups. A previous study has found that subclinical liver injury induced by PTU is common and usually transient[22]. Liver injury was not evaluated for duration in the present study but may be transient; however, because PTU-induced hepatotoxicity can be fatal[23], the management of patients with elevated serum levels of alanine and aspartate aminotransferase during antithyroid drug therapy is difficult. The rate of other adverse effects was also lower in the MMI15 group.

In conclusion, MMI at a dosage of 15 mg/day is as effective as MMI at 30 mg/day or PTU at 300 mg/day, and MMI at 15 mg/day is safer than MMI at 30 mg/day or PTU at 300 mg/day. A low daily dose of MMI is a safe initial regimen for antithyroid drug therapy.

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