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Original Article

Initial Treatment of Pediatric Graves' Disease with Methimazole: A Retrospective Follow-up Study

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Abstract. Antithyroid drugs are widely used in the therapy of Graves' disease (GD), and methimazole (MMI) is preferred for treatment of pediatric GD. The recommended initial dosage of MMI is 0.5–1.0 mg/kg/d for pediatric GD, although there are few studies on the optimal MMI dosage for initial treatment in children. We retrospectively compared the efficacy of different doses of MMI in 35 children with GD. Eight children were excluded due to lack of follow-up, etc. The remaining 27 children were divided into a high-dose group (HD; MMI≥0.7 (0.85 ± 0.13) mg/kg/d, n=8) and a low-dose group (LD; MMI<0.7 (0.51 ± 0.12) mg/kg/d, n=19), and we compared the time needed for the serum FT4 levels to normalize (≤1.6 ng/dl) between the groups. There were no significant differences between the FT4 levels (HD: 5.5 ± 2.8 ng/dl; LD: 5.0 ± 2.4 ng/dl p=0.59) or thyroid stimulating hormone receptor antibody levels (HD: 56.2 ± 29.3%; LD: 60.9 ± 27.2% p=0.69) between the groups before treatment. The mean time required to normalize the FT4 levels was 22.5 ± 7.4 d in the HD group and 28.8 ± 16.2 d in the LD group (p=0.30). In addition, no other factor influenced the time to efficacy of MMI. A dose of MMI<0.7 (0.51 ± 0.12) mg/kg/d appears to as effective as a higher dose in normalizing the serum FT4 level in children with mild or moderate GD.

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

Introduction

Antithyroid drugs (ATD) have been proposed as a first-line treatment for children with Graves' disease (GD) (1–3). Because recent reports have documented that propylthiouracil (PTU) is associated with severe side effects, methimazole (MMI) should be considered for treatment of these children (3–5).

Although the initial dose of MMI for pediatric GD is generally 0.5–1.0 mg/kg/d given once or twice daily (5), the most appropriate dose at the start of therapy is controversial. For adults with GD, MMI 15 mg/d is recommended for patients with mild and moderate disease, as this dosage was demonstrated to induce euthyroidism as effectively as 30 mg/d of MMI but with a

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significantly lower frequency of adverse events (6, 7). For adults with severe GD, 30 mg/d of MMI can induce euthyroidism quickly (within 3 mo) and is thus the recommended dosage (6, 7).

The optimal dosage of MMI for GD in children is not known. We retrospectively compared high and low doses of MMI in children to determine the most appropriate dosing for this age group.

Patients and Methods

Patients

Newly diagnosed patients with GD who were treated with MMI were included in the retrospective analysis. GD was diagnosed by clinical findings and the determination of serum T3, T4, free T4 (FT4), free T3 (FT3), thyroid stimulating hormone (TSH), TSH receptor antibody (TRAb) and ^{123}I- or ^{99m}Tc uptake. Patients who were older than 17 yr of age, who had severe complications, such as heart failure, or who were receiving glucocorticoid steroids or drugs that might influence thyroid function were excluded from the study.

Study design

This retrospective study was conducted at four medical institutions in Japan: Yaizu City Hospital in Yaizu, West Hamamatsu Medical Center in Hamamatsu, Fujieda City Hospital in Fujieda and Hamamatsu University School of Medicine in Hamamatsu, Japan. The Ethical Committees of Hamamatsu University School of Medicine and each hospital involved in the study approved the protocol. All eligible patients with untreated GD were seen at one of the four participating medical institutions from October 1991 to March 2009 and were treated with MMI. They were registered for the trial after informed consent was obtained from the patients' legal guardians. The patients were divided into the high-dose MMI group (HD; MMI≥0.7 mg/kg/d) or low-dose MMI group (LD; MMI<0.7 mg/kg/d) based on hospital records. A total of 35 patients with untreated GD were initially recruited for the study; 8 patients were excluded from the final analysis for the following reasons: could not be follow up (n=1), change in drug regimen or lack of efficacy (n=5) and drug dose was reduced before FT4 reached normal levels of ≤1.6 ng/dl (n=2). The reasons for changing the drug regimen included side effects in 2 patients (1 patient started on an MMI dose of 0.31 mg/kg/d and experienced a mild decrease in white blood cell count, mild liver function abnormalities and drug fever, and 1 patient started on a MMI dose of 0.50 mg/kg/d and experienced drug eruption) and lack of efficacy in 2 patients (1 patient's dose was increased to 1.2 mg/kg/d (45 mg/d), and 1 patient's dose was increased to 1.8 mg/kg/d (60 mg/d); the reason was unknown in 1 patient. Ultimately, 27 patients were evaluated (Fig. 1). Characteristics of the patients are shown in Table 1.

All patients had FT4 levels ≥1.7 ng/dl before ATD treatment. We compared the duration between the start of MMI start and normalization of thyroid function between the groups. Normalization of thyroid function was defined as FT4 levels of 0.8–1.6 ng/dl or T4 levels of 5–12 μg/dl (2 patients were followed by T4). After the serum FT4 level decreased to within the normal range, the MMI dosage was reduced to match the condition of each patient. Because FT3 and TSH levels require more time to reach normal levels than the FT4 level, it is difficult to analyze the results for FT3 and TSH, and therefore we used only the FT4 levels to define normalization of thyroid function. Remission was defined as a continuous euthyroid state for more than 1 yr without drugs. The dose of MMI was lessened over time, but it was not reduced before the FT4 or T4 levels reached normal ranges. After the FT4 or T4 levels reached normal ranges, the patients were given suitable doses of MMI to maintain normal thyroid hormone (TH) concentrations. Although some patients received treatment with L-thyroxine, which influenced

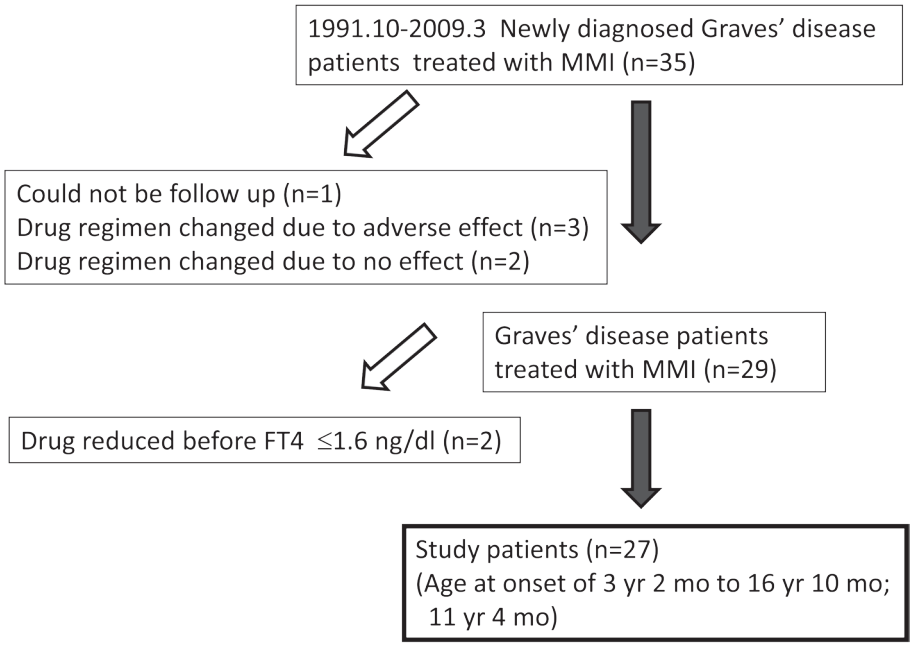

Fig. 1 Patient disposition.

the FT4 levels, no patient received this medication before the FT4 or T4 levels were normalized. When necessary, β-blocker therapy was given concomitantly if a patient experienced tachycardia. We also analyzed the time it took for the FT3 and TSH levels to normalize.

Serum FT4, FT3 and TSH were measured using a Roche ECLusys kit (Roche, Basel, Switzerland). Normal values and measurable ranges are as follows: FT4, 0.8–1.6 ng/dl (measurable range up to 7 ng/dl); T4, 5–12 μg/dl; and FT3, 3.1–4.9 pg/ml (measurable range up to 30 pg/ml). TRAb (normal range 0–10%) was assayed with TRAb-CT (Cosmic Corporation, Tokyo, Japan). Normal ranges were based on a previously published report (6). Normal ranges for the thyroid scan and uptake are as follows: 0.4–3.0% for ^{99m}Tc, 13% for ^{123}I (we used the 6-h uptake after oral administration, and patients had restricted intake of iodine-containing food for a week prior to the scan).

Statistical analysis

Data were analyzed statistically using the nonparametric *t*-test. Calculations were performed using StatView, version 5.0 (SAS Institute, Inc., Cary, NC, USA). Statistical significance was set at $p<0.05$.

Results

MMI efficacy was assessed in 8 children in the HD group and 19 children in the LD group. Mean age, sex, number of complications, initial FT3 value, initial FT4 value, initial TSH value, TRAb, ^{99m}Tc uptake and ^{123}I uptake before treatment showed no significant differences between the groups (Table 2).

The mean time required to achieve normal FT4 or T4 levels was 22.5 ± 7.4 d in the HD group and 28.8 ± 16.2 d in the LD group ($p=0.30$). Although differences between the groups were not statistically significant, children in the LD group tended to require more time to achieve normal FT4 levels than those in the HD group (Fig. 2). Initial FT3 level, age, TRAb, antithyroid peroxidase antibody (TPOAb) and complications did not influence the time needed for FT4 to

Table 1 Characteristics and clinical data of the patients

Patient No.	Age (yr)	Sex	With complication	Family history of Graves disease	Initial TSH Value (μU/ml)	Initial FT3 Value (pg/dl)	Initial FT4 Value (ng/dl)	Group of FT4 severity	TRAb (%)	Thyroid crisis	MMI initial dose (mg/d)	MMI initial dose (mg/kg/d)	Group of MMI dose	Period for FT4≤1.6 or T4≤12 (day)	Period for FT3≤4.9 (day)	Period for TSH≥0.5 (day)	Side effect	Remission
1	7.7	female	–	uncle	<0.01	27.9	>7.0	S	89	–	20	0.98	HD	25	15	160	–	remission
2	13.7	female	–	–	<0.01	24.5	>7.0	S	73	–	30	0.77	HD	19	27	76	–	remission
3	11.5	female	AD	mother	<0.01	>30	>7.0	S	26.7	–	20	0.78	HD	31	56	56	–	ND
4	12.1	female	–	–	<0.01	>30	5.4	M	94.2	–	30	0.71	HD	23			fever, rash	within 2 yr
5	11.3	female	–	–	<0.01	17.8	4.4	M	21.8	–	30	0.83	HD	22	57	98	–	ND
6	3.2	female	Turner	–	<0.01	12.5	3.7	M	48.7	–	20	1.10	HD	33	61	61	–	no remission
7	10.0	female	Turner	–	<0.01	14.4	2.68	M	69.9	–	20	0.84	HD	10			–	remission
8	7.0	female	GHD	–	<0.01	N D	2.33	M	26.3	–	15	0.78	HD	17			–	within 2 yr
9	8.6	female	Down, VSD, CPP	–	<0.01	6.2	1.9	M	33.7	–	5	0.23	LD	12	ND	62	–	no remission
10	13.8	female	–	–	<0.01	12.9	3.21	M	69.1	–	25	0.52	LD	25	21	180	nettle rash	within 2 yr
11	11.0	female	–	grandfather	<0.01	8.3	2.4	M	14.7	–	10	0.22	LD	35	35	98	–	remission
12	10.3	female	–	–	<0.01	27	>7.0	S	87	–	15	0.56	LD	31	77	108	rash	within 2 yr
13	11.8	female	–	–	<0.01	>30	>7.0	S	57.6	–	15	0.42	LD	14	112	112	–	within 2 yr
14	4.3	female	CPP	grandmother	<0.01	>30	>7.0	S	67.8	–	30	0.63	LD	30	58	78	–	ND
15	15.5	female	–	–	<0.01	>30	>7.0	S	79.4	–	30	0.52	LD	37	159	201	–	remission
16	14.9	female	–	–	<0.01	22.4	6.3	M	52.2	–	30	0.60	LD	47	128	165	–	ND
17	16.8	male	–	sister	<0.01	>30	5.9	M	36.1	–	30	0.45	LD	26	26	68	–	ND
18	14.2	female	Type1 DM	–	<0.01	17.8	5.6	M	86.9	–	30	0.51	LD	34	41	191	–	no remission
19	15.4	male	–	–	<0.01	N D	5.32	M	44.4	–	30	0.56	LD	21	ND	ND	–	remission
20	11.8	male	–	–	<0.01	22.9	5.25	M	77.4	–	20	0.51	LD	12	ND	ND	muscle pain	within 2 yr
21	14.3	female	–	–	<0.01	15.7	4.55	M	53.3	–	40	0.64	LD	77	ND	ND	–	ND
22	7.8	female	–	–	<0.01	>30	4.26	M	66	–	15	0.58	LD	17	ND	ND	–	within 2 yr
23	11.8	female	JIA	–	<0.01	12.8	4.2	M	130	–	30	0.62	LD	17	ND	ND	nettle rash	remission
24	10.8	female	–	–	<0.01	15.6	3.9	M	69.7	–	15	0.44	LD	51	ND	ND	muscle pain	within 2 yr
25	9.6	female	Down	–	<0.01	9.6	2.7	M	30.4	–	15	0.59	LD	28	28	44	nettle rash	ND
26	14.4	female	–	–	<0.01	14.8	2.67	M	75.7	–	30	0.59	LD	21	ND	ND	itching	remission
27	11.8	female	WPW	–	<0.01	6.8	2.48	M	25.1	–	20	0.41	LD	13	22	32	–	remission

AD, atopic disease; GHD, growth hormone diffeciency; VSD, ventricular septal defect; CPP, central precocious puberty; Type1 DM, Type 1 diabetes mellitus; JIA, juvenile idiopathic arthritis; S, severe FT4 group; M, mild or moderate FT4 group; HD, MMI high dose group (≥0.7 mg/kg/d); LD, MMI low dose group (<0.7 mg/kg/d); ND, no data.

Table 2 Comparison of clinical data between the HD and LD groups

	HD	LD	p value
Number of patients	8	19	
Mean age ± SD (yr)	9.5 ± 3.4	12.0 ± 3.1	0.08
Sex male	0	3	
female	8	16	
Number with complications	4 (50%)	5 (26.3%)	
MMI dose ± SD (mg/kg/d)	0.85 ± 0.13	0.51 ± 0.12	<0.0001
Initial FT3 Value ± SD (pg/dl)	21.8 ± 6.9 (n=7)	18.0 ± 7.9 (n=18)	0.28
Initial FT4 Value ± SD (ng/dl)	5.5 ± 2.8	5.0 ± 2.4	0.59
Initial TSH Value ± SD (μU/ml)	<0.01	<0.01	
TRAb ± SD (%)	56.2 ± 29.3	60.9 ± 27.2	0.69
Tc Uptake	51.1 (n=1)	46.6 ± 29.9 (n=9)	
^{123}I Uptake	65.9 ± 9.1 (n=3)	37.8 ± 12.6 (n=2)	0.06
Period in hospital ± SD (day)	31.4 ± 3.4	26.0 ± 23.9	0.63
Number of remission	3/4	6/8	*

*HD: introduced to another hospital (n=2) within 2 yr after diagnosis of GD (n=2). LD: introduced to another hospital (n=5) within 2 yr after diagnosis of GD (n=6).

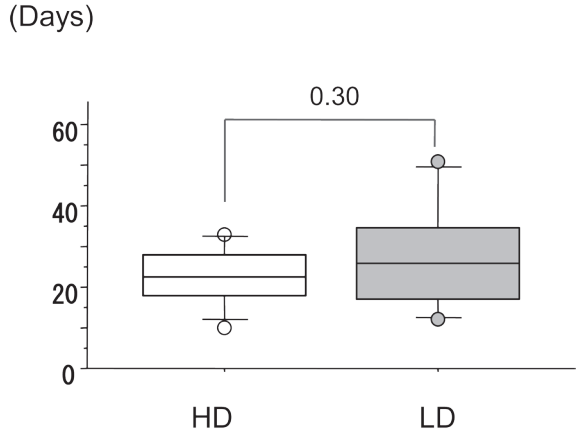

Fig. 2 Comparison of treatment efficacy between the highdose (HD; ≥0.7 mg/kg/d) and low-dose (LD; <0.7 mg/kg/d) MMI groups among children with Graves' disease. Efficacy was defined as achieving normal FT4 levels (≤1.6 ng/dl) or T4 levels (≤12 μg/dl). The numbers above the columns represent the p values for the nonparametric *t*-test analysis of the MMI HD and LD groups. The bars in the columns indicate the mean time needed to achieve normal FT4 levels.

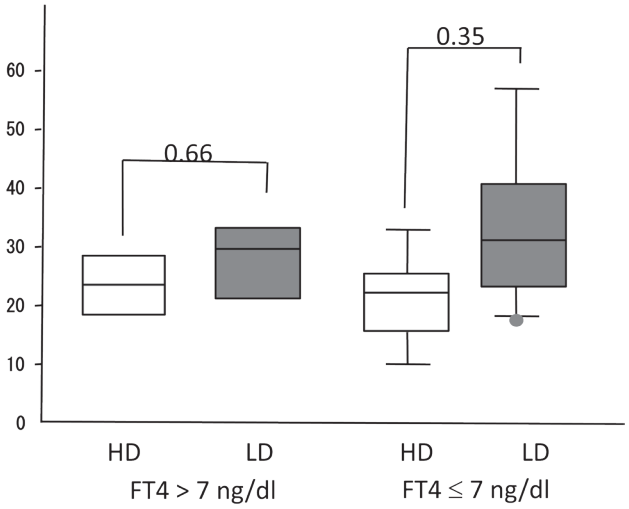

Fig. 3 Comparison of treatment efficacy between the high-dose (HD; ≥0.7 mg/kg/d) and low-dose (LD; <0.7 mg/kg/d) MMI groups among children with Graves' disease based on the initial FT4 levels. The bars in the columns indicate the mean time needed to achieve normal FT4 levels. The severe FT4 group included patients that had an initial FT4≥7 ng/dl, and the mild FT4 group included patients that had an initial FT4<7 ng/dl.

normalize (data not shown).

At the time that FT4 normalized, the FT3 levels in the HD and LD groups were 5.3 ± 0.9 and 6.4 ± 1.4 pg/dl, respectively (p=0.14). The TSH levels were below 0.02 μU/ml in both groups. Days in the hospital and remission rates did not differ significantly between the HD and LD groups. Side effects occurred in 1 (12.5%) patient in the HD group and 7 (36.8%) patients in the LD group. All side effects were minor, with the most common effect being a rash.

The FT3 levels reached normal ranges in 43.2 ± 20.8 d in the HD group and 64.3 ± 48.3 d in the LD group (p=0.37), and the TSH levels reached normal ranges in 90.2 ± 42.3 d in the HD group and 111.6 ± 59.1 d in the LD group (p=0.48). The FT3 and TSH levels took more time to normalize than the FT4 levels. Thus these results include patients whose MMI dose was lowered before the FT3 or TSH levels became normal. After the FT4 levels normalized, the dosages were determined individually by the treating physicians, and there were differences among the patients.

We also divided the patients into 2 groups based on the severity of the initial FT4 level and analyzed which patient group should receive HD MMI based on the time of efficacy of treatment (i.e., achieving normal FT4 levels). In the severe FT4 group (initial FT4≥7), efficacy occurred in 25.0 ± 6.0 d in the HD group and 28.0 ± 9.8 d in the LD group (p=0.66). In the mild FT4 group (initial FT4<7), efficacy occurred in 21.0 ± 8.5 d in the HD group and 29.1 ± 17.8 d in the LD group (p=0.35; Fig. 3).

Discussion

Because of the risk of thyroid cancer associated with radioiodine therapy and the difficulty of performing surgery, many endocrinologists use an ATD (antithyroid drug) as the nitial treatment for GD in childhood, even if the remission rates are low (2, 5, 13–16). In a survey of members of the European Thyroid Association (ETA) and of the European Society for Pediatric Endocrinology (ESPE), 99% of respondents reported that an ATD was the initial treatment choice for children with uncomplicated GD (3).

In Japan, both MMI and PTU have been used as ATDs. However, PTU has a much higher rate of adverse effect in pediatric GD, including a high prevalence of increased antineutrophil cytoplasmic antibodies (14).

In April 2009, the Lawson Wilkins Pediatric Endocrine Society raised concerns about serious hepatic toxicities (even requiring liver transplantation) and death among children with GD receiving PTU. These problems have not been reported with MMI use in children (4). Thus, MMI has become the more popular choice for treatment of GD in children. In addition, the long duration of action of MMI allows for once-daily dosing, which helps increase compliance with treatment (12).

The recommended dosage for initial therapy with MMI is 0.5–1.0 mg/kg/d for children with GD (3), but there is little evidence to support this dosage. More than half of the pediatric endocrinologists and thyroidologists responding to a questionnaire survey indicated that they started MMI for pediatric GD at 1 mg/kg/d (1). Therefore, if the dose is based on body weight, many children will start near 30 mg/d and exceed the dose recommended for adults.

Several studies have reported on doses of MMI for adults with GD. Several reports have compared 15 mg/d and 30 mg/d of MMI and concluded there is no difference between dosages in mean time to euthyroidism (6–9). However, it is generally recommended that patients with severe GD start at 30 mg/d of MMI to induce euthyroidism quickly (6–9). It has been demonstrated that the frequency of adverse events is lower with 15 mg/d than with 30 mg/d (6, 7, 10, 11), and we thought the lower dosage might also be appropriate for children with GD.

In our study, there were no significant

differences in the time needed to achieve normal FT4 levels between the HD and LD groups. In addition, hospitalization time and remission rates did not differ between the groups. Thus, there does not appear to be any benefit to using a higher dose of MMI in children. In the LD group, the mean dose of MMI was 0.51 mg/kg/d. Thus, we believe that a starting dose of MMI of 0.5 mg/kg/d for children with GD is sufficient. Someya *et al.* (17) reported no differences in time to efficacy between HD (MMI≥0.7 mg/kg/d) and LD (MMI<0.7 mg/kg/d) groups, with efficacy achieved in 1.8 ± 1.3 months in the HD group (n=24) and 2.0 ± 1.3 months in the LD group (n=23). However, they did not report the FT4 levels, and no information was provided regarding how they defined efficacy. In their research, those receiving LD MMI took a slightly longer time to achieve efficacy, but as with our study, the results did not differ significantly between groups. It is known that there are many factors related with remission rate in treatment of GD. Our data seem to indicate there was at least no strong relation between remission rate and initial MMI dose.

For pediatric patients, the initial term for euthyroidism is important. In Japan, almost all children who develop GD are treated as inpatients at first. Their school life and physical activity are also restricted before euthyroidism occurs. Until now, there was a tendency to use a high dose of MMI, which can induce euthyroidism quickly, to shorten the inpatient stay. However, our data shows no significant difference in time to euthyroidism between the high and low doses of MMI. Because all types of therapy should be initiated at the minimum effective dose, a lower dose of MMI may be more appropriate for children with mild or moderate GD.

In terms of severe GD, adults have been generally prescribed a higher dosage (i.e., MMI 30 mg/d) (7). We had a few patients with severe GD (initial FT4≥7), and there was no clear differentiation between the HD and LD in this group. This finding suggests that even in children with severe disease, a low dose of MMI can be used to normalize thyroid function safely. However, our study included only a small number of patients, especially of severe patients, and was retrospective in design, which limits the ability to generalize these findings to larger populations. Further prospective studies may more precisely clarify the optimal dose of MMI for children with GD.

Conclusion

For children with mild or moderate GD, an initial dose of MMI<0.7 (mean 0.51 ± 0.12) mg/kg/d is as effective as a higher dose (≥ 0.7 (0.85 ± 0.13) mg/kg/d) in normalizing the serum FT4 level.

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