Survey of the actual administration of thiamazole for hyperthyroidism in Japan by the Japan Thyroid Association

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Abstract. To clarify the actual administration of thiamazole (MMI), the first choice of antithyroid drugs, the actual therapy provided by the Japan Thyroid Association (JTA) members for the following conditions was surveyed. The subjects included adult patients, pregnant women, and pediatric patients with Graves’ disease who visited each medical institution from September 2019 to February 2020. Initial doses, frequency of administration, maintenance doses, maximum doses, consultation intervals for pregnant women, and dosages administrated to breastfeeding mothers were surveyed. The total number of cases collected was 11,663. Administration of 15 mg once a day was the most common initial therapy, constituted 74.4% (2,526/3,397 cases) of adults, 33.8% (44/130) of pregnant women, and 50.8% (61/120) of children. The maintenance dose before discontinuation was equivalent to 2.5 mg/day in 52.3% (3,147/6,015). The most common maximum dose for adults and children was 30 mg/day, administrated to 57.5% of adults (223/388) and 59.6% (28/47) of children; for pregnant women, it was 15 mg/day, administrated to 71.1% (27/38). The most common consultation interval for pregnant women was every four weeks (32.1%, 341/1,063). In lactating mothers, the dose was 10 mg/day or less in 366 of 465 cases (78.7%). Breastfeeding was also allowed 4–6 hours after the administration of 15–20 mg/day in 69 patients (14.8%). Breastfeeding was prohibited in 26 patients (5.6%). In conclusion, initial MMI therapy was started with 15 mg once a day in most patients, and MMI was also administrated to lactating mothers following the Graves’ disease treatment guidelines by the JTA.

Key words: Graves’ disease, Hyperthyroidism, Thiamazole, Antithyroid drugs

THE MAIN TREATMENT of Graves’ disease is antithyroid drugs (ATDs) in Asia and Europe, whereas in the United States, it used to be radioactive iodine (RAI) therapy in most adult patients. However, recent reports showed that more than half of patients received ATD treatment in the United States [1, 2], and now, ATDs are the main treatment for Graves’ disease worldwide. The safety and effectiveness of thiamazole (MMI), which is the first choice of ATDs, are becoming more important.

As ATDs, MMI and propylthiouracil (PTU) have been used for the medical treatment of hyperthyroidism (mainly Graves’ disease) in Japan. In 2006, to present evidence-based medical treatment, the Japan Thyroid Association (JTA) published Guidelines for the Treatment of Graves’ Disease with Antithyroid Drugs, clearly stating that MMI is generally the first-choice ATD [3]. Then, a multicenter, randomized, clinical trial of the initial treatment of Graves’ disease was conducted to propose the details of the optimal initial dose of ATDs [4]. Reflecting this study, the Guidelines for the Treatment of Graves’ Disease 2011 (GDGL2011) recommended that the initial dose of MMI should be chosen according to thyroid function [5]. In 2019, a revised guideline, Guidelines for the Treatment of Graves’ Disease 2019 (GDGL2019), based on additional evidence, was published [6]. For pediatric patients, Guidelines for Childhood-onset Graves’ Disease were published in 2008 [7] and revised in 2016 [8]. Based on these guidelines, the detailed and proper use of ATDs has been clarified, including the initial dose and regimen, the decision to discontinue, and the management of breastfeeding mothers. Whereas more than half a century has passed since approval of both MMI (listed drug price in 1957) and PTU (listed drug price in 1967) in Japan, the instructed doses of the ATDs in their package inserts as prescription drugs have not changed and differ from the suggested treatments for Graves’ disease described in the
JTA guidelines. Therefore, the JTA should propose proper package insert instructions [9] according to accurate clinical data of the administration of MMI, which is the first-choice ATD. These proposals and data analyses contribute to the proper clinical practice of all clinicians in Japan and may also contribute to the practice of clinicians in other countries.

Materials and Methods

This survey was performed by questionnaires to the JTA members on the official website. The survey included one question asking if the respondent to the survey was an official specialist certified by JTA. The questionnaires also included opinions about the doses of the package insert of MMI tablets prepared by the pharmaceutical company. The subjects of the survey were patients with Graves’ disease who consulted the respondents of this survey and were administrated MMI tablets (5 mg/tablet) from September 2019 to February 2020. The classifications and items of this survey were the following. The first category of subjects was composed of patients treated initially. The surveyed items consisted of the initial doses and the frequency of administration at the initial treatment, including treatment for new-onset cases, as well as relapsed cases, in adults and the number of patients administrated each dose (Survey 1). The second category of subjects and the third category of subjects were pregnant female patients (Survey 2) and pediatric patients (Survey 3). The surveyed items were the same as for Survey 1. The fourth category was composed of subjects treated with maintenance doses of MMI and the number of patients administrated each dose. The maintenance dose was defined as the dose at which discontinuation of MMI was considered after 6 months of administration (Survey 4). The fifth category was composed of subjects treated with the maximum dose including patients refractory and resistant to the treatment. They included adults, pregnant women, and children. The questions included the maximum doses and the number of patients administrated each dose (Survey 5). Additional data included the interval between clinical visits during pregnancy and the number of pregnant patients (Survey 6). In lactating mothers, the dose of MMI and the timing relationship between administration and breastfeeding were surveyed (Survey 7) (Supplemental Material 1) [10]. On the dedicated website, replies were received during the period from March 16, 2020, to May 15, 2020.

Data are expressed as the numbers of subjects and proportions with incidence rates. Significance was calculated with the χ² test or Fisher’s exact test. A p-value <0.05 was considered significant. Statistical analysis was calculated by software JMP version 14.0.0 (SAS Institute Inc., Cary, NC, USA).

This study was approved by the Ethics Committee of Ito Hospital (approval number: 276).

Results

Characteristics of respondents

The responses were provided by 110 members of the JTA, and the total number of patients collected in this survey was 11,663. As for the responders, 60 (54.5%) were JTA-certified specialists, 48 (43.6%) were non-specialists, and 2 (1.8%) were unknown. Opinions about the content of the package insert for MMI were as follows. The number of responders who were not against the current package insert was 13 (11.8%). The number of participants who advocated that correction of the dose or frequency of administration was necessary was 73 (66.4%). The number of participants who identified a problem but did not want correction was 19 (17.3%), that of others was 3 (2.7%), and not available was 2 (1.8%). The percentage of responders who responded that the dose and frequency of administration needed to be changed was 46 (76.7%) for specialists and 27 (56.3%) for non-specialists, significantly higher in specialists (p = 0.009).

Initial dose and frequency of administration

The initial dose in adult cases (Survey 1) (n = 3,397) was 15 mg/day in 2,636 cases (77.6%), 30 mg/day in 242 cases (7.1%), and others in 519 cases (15.3%) (Fig. 1A). MMI 15 mg/day (n = 2,636) was administrated once a day in 2,526 cases (95.8%). MMI 30 mg/day (n = 242) was administrated once a day in 139 cases (57.4%), in divided doses twice a day in 90 cases (37.2%), and in divided doses 3 times a day in 13 cases (5.4%) (Fig. 1B). The initial doses for pregnant women (Survey 2) (n = 130) and children (Survey 3) (n = 120) were similar to those of adult cases. MMI 15 mg/day was the most common dose of MMI, administrated to 45 (34.6%) cases of pregnant women and to 64 (53.3%) cases of children (Figs. 2A and 3A), and 15 mg/day of MMI was administrated mostly once a day in 44 cases (97.8%) and in 61 cases (95.3%) (Figs. 2B and 3B), respectively. As for higher doses of MMI, 30 mg/day was administrated to 23 pregnant women, once a day in 3 cases (13.0%), in divided doses twice a day in 10 cases (43.5%), and in divided doses 3 times a day in 10 cases (43.5%) (Fig. 2B). As for children, 20–30 mg/day of MMI was administrated to 8 children, once a day in 3 cases (37.5%) and in divided doses twice a day in 5 cases (62.5%) (Fig. 3B).

The data of the survey were classified according to the
respondents into two groups, specialist and non-specialist, and are shown in Supplemental Figs. 1, 2, and 3. The percentage administrated divided doses 3 times a day and the percentage of MMI 30 mg/day in adults were significantly lower for specialists than for non-specialists (1.5% (44/2,906) vs. 8.6% (42/491), p < 0.001, 6.7% (196/2,906) vs. 9.4% (46/491), p = 0.04, respectively) (Supplemental Fig. 1).

**Maintenance dose**

The information of maintenance dose was obtained for 6,015 patients (Survey 4) (Fig. 4). A dose equivalent to

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**Fig. 1** Initial dose and frequency of administration in adults
A: Initial dose and frequency of administration, B: Frequency of administration of each dose
Data are expressed as the numbers of subjects and proportions with incidence rates (%).

**Fig. 2** Initial dose and frequency of administration in pregnant women
A: Initial dose and frequency of administration, B: Frequency of administration of each dose
Data are expressed as the numbers of subjects and proportions with incidence rates (%).
2.5 mg/day accounted for the majority and was administered in 3,147 cases (52.3%) (2.5 mg once daily: \(n = 117\) and 5 mg every other day: \(n = 3,030\)). Other doses were administered to significantly more subjects by specialists than by non-specialists [28.9% (1,433/4,957) vs. 9.2% (94/1,026), \(p < 0.0001\)] (Supplemental Fig. 4).

**Maximum dose**

The maximum doses in adult cases (\(n = 388\)), pregnant women (\(n = 38\)), and children (\(n = 47\)) are shown in Figs. 5A, B, and C, respectively (Survey 5). The most common maximum dose for adults and children was 30 mg/day, administrated to 57.5% (223/388) and 59.6% (28/47), respectively, and for pregnant women, it was 15 mg/day, administrated to 71.1% (27/38). The specialists chose higher maximum doses (Supplemental Fig. 5).

**Consultation interval for treatment during pregnancy**

The consultation interval of pregnant women (Survey Fig. 3 **Initial dose and frequency of administration in children**

A: Initial dose and frequency of administration, B: Frequency of administration of each dose

Data are expressed as the numbers of subjects and proportions with incidence rates (%).
6) \((n = 1,063)\) was surveyed. The most common consultation interval of pregnant women was every four weeks in 341 cases (32.1%), followed by changed according to the period of gestational weeks in 165 cases (15.5%) (Fig. 6). The Interval of every 4 weeks was the most frequent for both specialists and non-specialists (Supplemental Fig. 6).

**Dosage during breastfeeding**

The administration dosage during breastfeeding (Survey 7) \((n = 465)\) was 5 mg/day in 102 cases (21.9%) and 10 mg/day in 264 cases (56.8%). Breastfeeding was also allowed 4–6 hours after the administration of 15–20 mg/day of MMI in 69 patients (14.8%), whereas breastfeeding was avoided in 26 cases (5.6%) (Fig. 7). The proportion of patients who avoided breastfeeding was significantly lower among specialists \([3.8\% (15/394) vs. 15.5\% (11/71), p = 0.0002]\) (Supplemental Fig. 7).

**Discussion**

This paper reported the results of the first survey of
the actual administration of MMI preparations in Japan and provided valuable information. The actual initial dose, frequency of administration, and administration in breastfeeding were compatible with the JTA guidelines for the treatment of Graves’ disease and not with the package insert [9].

Regarding the initial treatment of adults, in the package insert, the initial dose is 30 mg/day divided into 3 to 4 times per day, whereas in the GDGL2011 [5], the initial dose is recommended to be determined according to thyroid function: 15 mg/day in mild cases (e.g., free T4 less than 5 ng/dL) and 30 mg/day in severe cases (e.g., free T4 7 ng/dL or higher), because administration of high-dose MMI increased the frequency of mild [4] and severe [11] adverse events, and administration of low-dose MMI was sufficient to control mild hyperthyroidism. In addition, GDGL2019 [6] proposed the co-administration of potassium iodide (KI) with MMI 15 mg for severe hyperthyroidism (free T4 5 ng/dL or higher). This combination therapy provided early control of thyroid function, avoiding high-dose use of MMI and reducing the risk of adverse events [12, 13]. In the current study, the most common initial dose was 15 mg/day, at approximately 80%, and it was thought that our intention in producing and disseminating the treatment guidelines is well appreciated and practiced clinically. Since thyroid function and the administration of KI were not included in the current study, the appropriate alteration of dose according to thyroid function and the combination with KI were not examined and need further study. Regarding single and multiple daily doses of MMI, GDGL2011 proposed administration once a day, because it had been reported that a single dose therapy provides a sufficient antithyroid effect [14, 15], and adherence is superior to multiple-dose therapy [16]. In the current study, a single dose accounted for 96% at 15 mg/day and 57% at 30 mg/day, and it seems that the single-dose method indicated by the guideline is pervasive. The effects of multiple divided doses on controlling thyroid function and adherence have not been investigated in a large number of cases. In the report [17] that examined the duration of the effect in a perchlorate release study after taking MMI, 77% of patients in the MMI group were controlled with a single dose, two doses were required in 21%, and three doses were required in only 2%. Considering adherence, administration once or twice a day would be reasonable.

The initial dose and frequency of administration in pregnant cases in the package insert were 15–30 mg/day divided into 3 to 4 times per day. In GDGL, there is no recommended dosage. In the current study, the main dose was 15 mg/day and 30 mg/day in 35% and 18% of pregnant cases, respectively. Most of the doses were once a day for 15 mg/day, which was the same trend as in adults, whereas other doses were administrated to half of the cases (n = 62, 48%), more frequently than expected, suggesting that various doses and dividing methods were used in pregnant women depending on the weeks of pregnancy and the disease status. To understand the actual usage and to clarify the appropriate MMI treatment of pregnant women with Graves’ disease, it will be necessary to survey more detailed dosages of MMI and the use of other drugs, i.e. PTU and KI.

As for children, the dose change according to age is described in the package insert: for 5–10 years old, 10–20 mg/day; and for 10–15 years old, 20–30 mg/day, administrated in divided doses 2 to 4 times a day. According to the guidelines for the treatment of pediatric
Graves’ disease 2016 [8], the initial dose is 0.2 to 0.5 mg/kg/day, administrated once or twice a day. If the calculated dose from the body weight exceeds the adult dose, the adult dose (15 mg/day) is recommended. In the current survey, only 10% chose the initial dose calculated from body weight, and 15 mg/day was used in the majority. Pediatric Graves’ disease generally develops after junior high school [18]. The initial dose may have been similar to that of adults because many children after junior high school have the same physique as adults. The frequency of administrated in children was consistent with the tendency in adults.

The maintenance dose in the medical package insert is 5–10 mg/day, with administration once or twice a day. However, the maintenance dose that can maintain normal thyroid function was expected to vary depending on the severity in each patient. Therefore, in the present study, the maintenance dose was defined as the “dose considering discontinuation of MMI after treatment for 6 months”, corresponding to the minimum maintenance dose in GDGL. This survey showed that a dose equivalent to 2.5 mg/day was selected for half of the cases, which was consistent with the GDGL recommendation. The frequency of clinical use of this small dose is high in Japan, and a new tablet form with 2.5 mg of MMI per tablet was officially approved, and listed in drug price in December 2020, and available for clinical use in Japan.

The package insert states that, when the symptoms are severe, 40–60 mg/day per day is used in adults. In the GDGL, there is no recommended maximum dose for adults and pregnant women. In the current survey, the most common maximum dose was 30 mg/day, and 100 mg/day was the highest dose in adults. Concerning pregnant women, 15 mg/day was frequent (at 71%), and the highest maximum dose was 40 mg/day, which was lower than that in adults. The upper limit of the MMI dosage is unknown. In a small study of high-dose use, the dose ranged from 75 to 120 mg [19]. In a national survey of thyroid storm in Japan, the median dosage was 30 mg/day, ranging from 5 to 120 mg/day [20]. The initial dose for thyroid storm recommended is 60 mg/day in the thyroid storm guidelines in Japan [21]. A method of continuously using a large amount of MMI of 40 mg to 100 mg to increase the remission rate had been used in the past [22-28]. Systematic reviews concluded that there is no evidence that high doses increase remission rates, and that the frequency of side effects increases significantly [28, 29]. When using a higher dose of MMI, it is necessary to pay more attention to the onset of adverse events, and the transition to definitive treatment with thyroidec- tomy or RAI therapy should be recommended. The Japanese Guidelines for Childhood-onset Graves’ Disease states that the dose should be double the initial dose (to 30 mg/day) in severe cases. In the current survey, in 80% of cases, the dose was up to 30 mg/day, but there were cases in which the dose was higher than 30 mg/day, which may be due to similar body features to adults.

Regarding the consultation interval of pregnant women, the package insert states, to avoid excess suppression of thyroid function during pregnancy, thyroid function tests should be performed every two weeks, and the minimum necessary dose should be administrated. The JTA guidelines provided no recommendation for the consultation interval. In the current study, the consultation interval of pregnant women was every 4 weeks in 32%, which is compatible with ATA guidelines [30], and it was changed depending on the pregnancy week in 16%. The package insert suggests a uniform interval of every two weeks, which differs from actual clinical practice.

Regarding breastfeeding, the package insert states that it is desirable to avoid breastfeeding while taking this drug. GDGL2019 states that MMI up to 10 mg can be administrated without checking the thyroid function of the infant. If a larger dose is administrated, the thyroid function of the infant should be checked, or it is recommended to give alternate nutrition for about 4 to 6 hours after taking MMI because the concentration in breast milk is high during that period. In the current survey, 94% of the cases were permitted breastfeeding, consistent with the above GDGL2019 statements [6]. On the other hand, 6% of the cases were not permitted breastfeeding, with as many as 15% of non-specialists not permitting breastfeeding. Considering the benefits of breastfeeding [31], unreasonable and unnecessary breastfeeding restrictions may lose the benefits for the mother and child, and, therefore, it is considered that the information and recommendations of GDGL should be propagated.

This survey has the following limitations and challenges. First, in GDGL2019 [6], it was proposed 1) to use KI in combination with MMI 15 mg for severe hyperthyroidism, and 2) to avoid MMI in the early period of pregnancy, taking into account teratogenicity [32], by discontinuation of MMI and/or using PTU and/or KI [33]. To clarify the actual usage of MMI for Graves’ disease, it will be necessary to survey the use of these drugs. Second, since children have different ages and physiques depending on the case, a more detailed survey including age and physique is required to understand the actual status of MMI use in children. Finally, since patients with Graves’ disease are treated by general physicians who are not members of JTA, it will be necessary to include general physicians in the survey in the future. We need to disseminate the Graves’ disease
treatment guidelines not only among JTA members, but also among general physicians. The package insert is the drug information that is readily available to everyone. If a physician with reference to the current package insert, for example, prescribes unnecessarily high doses (such as 30 mg/day) for mild Graves’ disease, it could result in unnecessary exposure to a high risk of adverse events. Revisions to the package insert will be considered for the safe and effective administration of MMI, in addition to propagating the Graves’ disease treatment guidelines.

Conclusion

The most common MMI regimen was 15 mg once a day for initial treatment, and approximately 90% of postpartum patients treated with MMI were permitted breastfeeding in concordance with the guidelines for the treatment of Graves’ disease by the JTA.

Acknowledgments

This survey was commissioned by the JTA. We would like to thank the cooperation of the members presented on the website of JTA (http://www.japanthyroid.jp/common/20210421_thiamazole.pdf). The authors belong to the following institutes: Department of Internal Medicine, Ito Hospital (Natsuko Watanabe and Jaeduk Yoshimura Noh), Department of Internal Medicine, Kuma Hospital (Takashi Akamizu), and Department of Internal Medicine, Division of Endocrinology and Metabolism, Gunma University Graduate School of Medicine (Masanobu Yamada).

Authors’ Disclosure Statements and Funding Statements

There are no conflicts to disclose and there is no funding information to declare.

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