INTERNAL MEDICINE

□ ORIGINAL ARTICLE □

Successful Re-administration of Low-dose of Methimazole (MMI) in Graves' Disease Patients Who Experienced Allergic Cutaneous Reactions to MMI at Initial Treatment and Had Received Long-term Propylthiouracil (PTU)

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Abstract

Objective When patients with Graves' disease show severe allergic cutaneous reactions, physicians often suggest that they undergo radioiodine therapy instead of receiving propylthiouracil (PTU), another antithyroid drug, because anti-neutrophil cytoplasmic antibody (ANCA)-related vasculitis can occur with PTU, especially with long-term use. However, some patients refuse radioiodine therapy and chose PTU. Sometimes PTU treatment may be prolonged. Since the frequency of adverse effects of methimazole (MMI) is dose-related, there is a possibility that we can re-administer a low dose without adverse effects to patients well-controlled with PTU who once experienced an allergic reaction to MMI.

Methods I prospectively re-administered a low dose of MMI to patients who previously experienced an allergic reaction to MMI at initial treatment. The dose of re-administered MMI ranged from 5 mg twice a week to 5 mg daily.

Patients Nine patients with Graves' disease who developed urticaria at initial treatment with MMI and had been treated with PTU for 6 to 21 years were recruited.

Results Eight of the 9 patients were successfully controlled with MMI without allergic cutaneous reactions. Only one patient felt itchiness 2 days after switching to MMI. However, skin change was not observed.

Conclusion If the patients show allergic cutaneous reactions as a side effect of MMI at the initial treatment for Graves' disease, then there is a strong possibility that such patients can tolerate a low dose of MMI without adverse effects after the disease activity has subsided.

Key words: Graves' disease, methimazole, propylthiouracil, adverse effect, re-administration

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Introduction

Graves' disease management guidelines of the Japanese Thyroid Association recommend that methimazole (MMI) should be used in every patient with Graves' disease as the first-choice drug except for during the first trimester of pregnancy. The recommendation is the same as in the United States (1). However, when patients with Graves' disease show an allergic skin reaction to MMI, not all patients will consequently accept other treatments, such as radioiodine therapy or thyroidectomy. Even if the thyroid function may have been controlled by propylthiouracil (PTU) without adverse effects, some patients refuse a change of treatment. Since anti-neutrophil cytoplasmic antibody (ANCA)-related vasculitis can occur with PTU, especially with long-term use (2), physicians do not want to administer PTU for a prolonged period. On the other hand, it is known that the frequency of adverse effects of MMI is dose-related (3-5). There is a possibility that we can re-administer a low dose

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Table. **Patients' Data at the Diagnosis of Graves' Disease and on Re-exposure to MMI.**

		At the diagnosis of Graves' disease									On re-exposure to MMI					
Patient	Sex	Age	FT4 (ng/dL)	FT3 (pg/mL)	TSH (μ IU/mL)	TRAb[c]	Thyroid volume (g)	The daily dose of MMI (mg)	Course	Treatment period (years)‖	Age	FT4[e] (ng/dL)	TSH[e] (μ IU/mL)	TRAb[d] (IU/L)	Dosage of PTU (mg)	The daily dose of MMI
1	F	47	4.5[a]	9.9[a]	<0.05[a]	6.1[d] IU/L	20	30	relapse	6	53	1.26	1.08	<0.3	25	5 mg every second day
2	F	36	2.95[a]	13.26[a]	<0.003[a]	69%	31.7	30	exacerbation by dose reduction	8	43	1.54	0.99	0.86	50	5 mg every second day
3	F	35	-	-	-	-	100	30	exacerbation by dose reduction	8	42	1.33	1.24	1.03	200	5 mg
4	F	30	2.27[a]	11.52[a]	<0.003[a]	-	-	15	relapse	9	39	1.2	0.73	0.64	50	5 mg every second day
5	F	65	1.98[a]	-	<0.003[a]	19.50%	-	5	relapse	10	75	1	2.55	1.65	25	5 mg twice a week
6	F	32	-	-	-	-	-	15	exacerbation by dose reduction	10	44	1.13	1.3	6.02	50	5 mg every second day
7	F	31	-	-	-	-	9.5	30	exacerbation by dose reduction	12	45	0.9	0.87	4.01	50	5 mg every second day
8	F	41	3.01[b]	7.3[b]	<0.07[b]	31.60%	25.5	20	relapse	14	55	1.36	2.24	<0.3	50	5 mg every second day
9	F	15	4.79[b]	25.5[b]	<0.05[b]	83.90%	32.3	30	relapse	21	36	1.42	4.67	3.27	50	5 mg every second day

a: TSH, FT4, and FT3 were measured employing ARCHITECT TSH, FT4, and FT3 assays, respectively (Abbott Co., Tokyo, Japan). Normal range: TSH (0.30-5.00μIU/mL), FT4 (0.70-1.60 ng/dL), FT3 (1.70-3.70 pg/mL)

b: TSH, FT4, and FT3 were measured employing AxSYM TSH, FT4, and FT3 assays, respectively (Dainabot Co., Tokyo, Japan). Normal range: TSH (0.40-4.50μIU/mL), FT4 (0.75-1.80 ng/dL), FT3 (2.30-4.50 pg/mL)

c: TRAb was measured with TSH receptor antibody assay kit (RSR Ltd., Cardiff, UK). Normal range: TRAb <15%

d: TRAb was measured with an Elecsys TRAb assay (Roche Diagnostics GmbH, Mannheim, Germany). Normal range: TRAb < 1.9 (IU/L)

e: TSH and FT4 were measured with an Elecsys TSH and FT4 assays, respectively (Roche Diagnostics GmbH, Mannheim, Germany). Normal range: TSH (0.30-5.00μIU/mL), FT4 (0.80-1.90 ng/dL)

‖ Thyroid volume was estimated by ultrasonography.

of MMI without adverse effects to patients well-controlled with PTU who previously experienced an allergic reaction to MMI. In this study, I prospectively re-administered a low dose of MMI to patients who previously experienced an allergic reaction to it at initial treatment in order to reduce the possibility of ANCA-related vasculitis with PTU.

Materials and Methods

Nine patients with Graves' disease who developed urticaria at initial treatment with MMI and had been treated with PTU for 6 to 21 years were recruited (Table). None of the patients took any drugs other than MMI as initial treatment of Graves' disease or had any allergies to food, drug or other allergens. All patients had widespread urticaria which developed within 30 days after starting MMI. Patient 9 required hospital admission for erythema multiforme-like eruption of the skin. Since urticaria was not resolved with antihistaminic drugs, MMI was replaced with PTU. The patients were treated with PTU for 6 to 21 years because 5 patients relapsed within a year after the discontinuation of PTU, and 4 patients worsened due to dose reduction. All patients were being well controlled with a low dose of PTU at the switch to MMI, and had refused radioiodine therapy and thyroidectomy since the initial treatment of Graves' disease.

The possibility of adverse effects, such as ANCA-related vasculitis, in long-term PTU treatment was explained to the patients. In addition, the possibility of allergic cutaneous reactions and agranulocytosis with re-administered MMI was explained. The patients were told that a low dose of MMI would not likely cause any adverse effects because the frequency of adverse effects caused by MMI is dose-related, and informed consent was obtained from all patients. Then the patients were prospectively switched to MMI. The dose of re-administered MMI ranged from 5 mg twice a week to 5 mg daily (Table).

Evaluation of the thyroid function

TSH, FT4, and FT3 were measured employing AxSYM TSH, FT4, and FT3 assays (Dainabot Co., Tokyo, Japan), respectively, at the diagnosis of Graves' disease in some patients. In the other patients, TSH, FT4, and FT3 were measured employing ARCHITECT TSH, FT4, and FT3 assays (Abbott Co., Tokyo, Japan), respectively, at the diagnosis of Graves' disease.

On re-exposure to MMI, TSH and FT4 were measured with Elecsys TSH and FT4 assays (Roche Diagnostics GmbH, Mannheim, Germany), respectively. TRAb was measured with a TSH receptor antibody assay (RSR Ltd., Cardiff, UK) or with a Elecsys TRAb assay (Roche Diagnostics GmbH). Normal ranges are described in Table.

Results

Eight of the 9 patients were successfully controlled with MMI without allergic cutaneous reactions. Only one patient (Patient 7) felt itchiness 2 days after switching to MMI. However, skin change was not observed. This patient resumed PTU. No patients showed other adverse effects, and 8 patients maintained a euthyroid state with a low dose of MMI.

Discussion

When patients with Graves' disease show allergic reactions at initial treatment with MMI, we have several alternative treatments for Graves' disease, such as radioiodine therapy, thyroidectomy, and the internal use of PTU. Because most Japanese patients prefer PTU rather than radioiodine therapy and thyroidectomy, we have no choice but to use PTU. Although we inform patients of the fact that PTU can cause fulminant hepatic necrosis and ANCA-related vasculitis (1, 2), especially with long-term use, some patients refuse to change their treatment after their thyroid functions are normalized with PTU. Many physicians treat such patient and continue to administer PTU. However, MMI treatment would be much safer for these patients.

In standard treatment of Graves' disease, we can gradually reduce the dose of MMI (15-30 mg/day to 5-2.5 mg/day). I hypothesized that patients may not show allergic reactions with a low dose of MMI even if they once experienced allergic reactions with a high dose of MMI at initial treatment because it is known that the frequency of adverse effects of MMI is dose-related. The results of this study supported this hypothesis.

Azizi et al. reported that long-term continuous MMI treatment in Graves' disease is safe and the risks of occurrence of cardiac or bone complications are equal to or less than those of radioiodine therapy (6). Additionally, Villagelin et al. suggested that prolonged low doses of MMI are an alternative choice for relapsed Graves' disease patients who refuse definitive treatment (7). In this study, 8 patients who were successfully controlled with MMI appeared to benefit from re-administration of MMI.

In conclusion, if patients show allergic cutaneous reactions as a side effect of MMI at initial treatment for Graves' disease, there is a strong possibility that such patients can tolerate a low dose of MMI without adverse effects after the disease activity has subsided. As a consequence, we can reduce the possibility of ANCA-related vasculitis with PTU in such patients. However, since the re-administration of MMI to patients who experienced an allergic reaction to it at initial treatment may be risky, we should pay very careful attention to severe adverse effects, such as agranulocytosis.

The author states that he has no Conflict of Interest (COI).

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