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ORIGINAL ARTICLE

Benefit of short-term iodide supplementation to antithyroid drug treatment of thyrotoxicosis due to Graves' disease

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Summary

Objective Combined treatment with anti-thyroid drugs (ATDs) and potassium iodide (KI) has been used only for severe thyrotoxicosis or as a pretreatment before urgent thyroidectomy in patients with Graves' disease. We compared methimazole (MMI) treatment with MMI + KI treatment in terms of rapid normalization of thyroid hormones during the early phase and examined the later induction of disease remission.

Design and patients A total of 134 untreated patients with Graves' disease were randomly assigned to one of four regimens: Group 1, MMI 30 mg; Group 2, MMI 30 mg + KI; Group 3, MMI 15 mg and Group 4, MMI 15 mg + KI. For easy handling, KI tablets were used instead of saturated solution of KI. KI was discontinued when patients showed normal free thyroxine (FT4) levels but MMI was continued with a tapering dosage until remission. Remission rate was examined during a 4- to 5-year observation.

Measurements Serum FT4, FT3 and TSH were measured by chemiluminescent immunoassays. TSH receptor antibody (TRAb) was assayed with TRAb-ELISA. Goitre size was estimated by ultrasonography.

Results After 2 weeks of treatment, normal FT4 was observed in 29% of patients in Group 1 and 59% ($P < 0{\cdot}05$) of patients in Group 2. Furthermore, normal FT4 after 2 weeks of treatment was observed in 27% of patients in Group 3 and 54% ($P < 0{\cdot}05$) of patients in Group 4. Similarly, FT3 normalized more rapidly in Groups 2 and 4 than in Groups 1 and 3. None of the patients showed an increase in thyroid hormones or aggravation of disease during combined treatment with MMI and KI. The remission rates in Groups 1, 2, 3 and 4 were 34%, 44%, 33% and 51%, respectively, and were higher in the groups receiving combined therapy but differences among four groups did not reach significance.

Conclusions Combined treatment with MMI and KI improved the short-term control of Graves' hyperthyroidism and was not associated with worsening hyperthyroidism or induction of thionamide resistance.

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Three major treatments, anti-thyroid drugs (ATDs), radioactive iodine therapy and surgery have been used to treat Graves' hyperthyroidism.[1] ATDs are the preferred first line treatment in most patients with Graves' hyperthyroidism in Japan[2] and Europe.[3] The goal of medical treatment is the rapid restoration of a euthyroid condition and early induction of disease remission.

Inorganic iodide is recommended in combination with ATDs when a rapid return to normal thyroid hormone levels is required, such as in the treatment of patients with severe thyrotoxicosis and in those undergoing urgent thyroidectomy.[1,4] In most studies, KI was cautiously administered for <10 days in combination with ATDs. However, the effectiveness was not shown to be superior to that of treatment with ATDs alone.[5–7] When iodide is used therapeutically, a saturated solution of potassium iodide (KI) or Lugol's solution has been used[7–9] but handling these solutions is inconvenient for patients. Combined therapy with ATDs + KI has not been administered routinely to patients with Graves' disease. Thus, there are no previous reports describing the use of this combination therapy as the first choice of standard therapy and the effect on disease remission has not been evaluated in general patients with Graves' hyperthyroidism.

In this study, we compared MMI treatment with MMI + KI treatment in terms of rapid normalization of thyroid hormones during the early phase and examined the later induction of disease remission, using KI tablets, which can be easily handled by patients.[10]

Patients and methods

Patients

Patients with untreated hyperthyroidism due to Graves' disease were recruited. Graves' disease was diagnosed according to the diagnostic guidelines of the Japan Thyroid Association (http://thyroid.umin.ac.jp/en/frame.html), based on clinical findings and the determination of serum free thyroxine (FT4), free triiodothyronine

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(FT3), thyroid stimulating hormone (TSH), TSH receptor antibody (TRAb) and/or radioactive iodine uptake. This study was conducted as a prospective trial, with an initial observation period of 12 weeks and subsequent follow-up of 4–5 years to examine disease remission.

Patients were randomly assigned to one of four regimens: Group 1, MMI 30 mg; Group 2, MMI 30 mg + KI; Group 3, MMI 15 mg and Group 4, MMI 15 mg + KI. One-hundred and sixty-nine patients were initially recruited for the study but 25 patients were excluded from the final analysis due to side effects of MMI, poor compliance, irregular follow-up examinations and dropout. The number of patients excluded for these reasons were 3, 4, 3 and 3 in the group receiving MMI alone and 5, 2, 1 and 4 in the group receiving MMI + KI, respectively. A total of 134 patients were finally analyzed including 35 in Group 1, 32 in Group 2, 30 in Group 3 and 37 in Group 4. Serum FT4, FT3 and TSH were assayed at 2, 4, 8 and 12 weeks.

For combination therapy, MMI and one KI tablet (50 mg of KI; 38·2 mg of iodide, Nichiiko Co. Ltd, Japan) were ingested simultaneously after breakfast, and KI tablets were discontinued when the patients' FT4 level returned to the normal range. Thereafter, a tapering dose of MMI continued until remission. MMI 30 mg and MMI 15 mg were administered as two divided doses and as a single dose, respectively. MMI was discontinued when patients remained euthyroid (normal FT4 and TSH) for at least 6 months under a minimum maintenance dose (MMI 5 mg every other day)[11] and patients were then followed for at least 1 year more. When patients remained euthyroid for at least 1 year without medication, we considered the disease in remission. The protocol was approved by the Ethical Committee of Kuma Hospital. All patients had untreated Graves' disease and each patient gave written informed consent prior to treatment.

Table 1. Patient groups and pertinent clinical data before treatment

Group	Drugs	No. examined	Male/ female	Age (years)	TRAb (%)	Goitre size (g)
1	MMI30 mg	35	8/27	40 ± 11	71 ± 19	36 ± 33
2	MMI30 mg + KI	32	9/23	38 ± 15	75 ± 17	37 ± 23
3	MMI15 mg	30	7/23	41 ± 14	70 ± 19	40 ± 31
4	MMI15 mg + KI	37	6/31	38 ± 15	78 ± 17	35 ± 19

Data are mean ± SD.

Laboratory

Serum FT4, FT3 and TSH were measured by chemiluminescent immunoassays with Architect kits (Abott, Japan). The normal values and measurable ranges are as follows: FT4, 9·03–20·64 pmol/l (measurable range up to 77·4 pmol/l), FT3, 2·63–5·72 pmol/l (measurable range up to 46·35 pmol/l) and TSH, 0·3–5·0 U/l. TRAb (normal range 0–15%) was assayed with TRAb-ELISA (Cosmic Corp, Japan).[12] Goitre size was estimated by ultrasonography as previously described.[13]

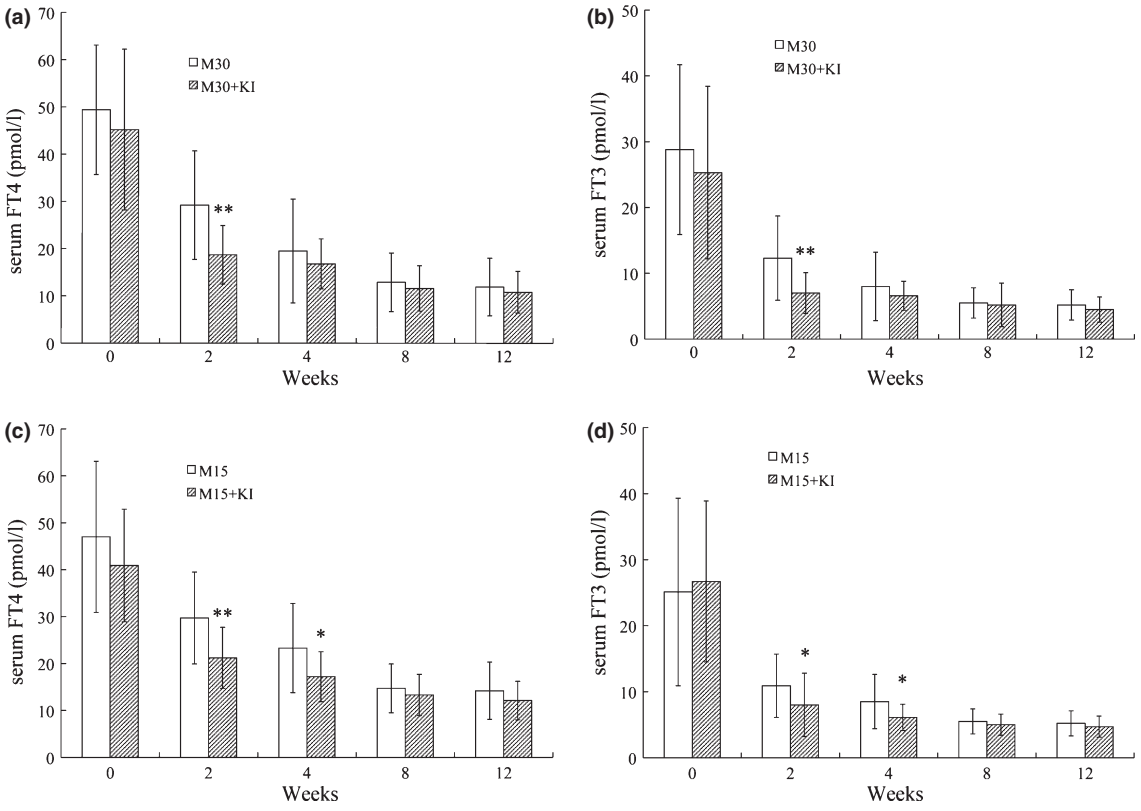

Fig. 1 Serial changes in serum FT4 and FT3 in four groups. Open column indicates MMI alone groups; Group 1 (MMI 30 mg) (a, b) and Group 3 (MMI 15 mg) (c, d). Shaded column indicates groups receiving a combination of MMI + KI; Group 2 (MMI 30 mg + KI) (a, b) and Group 4 (MMI 15 mg + KI) (c, d). Data are mean ± SD. Significantly different at $P < 0{\cdot}01$ (**) and $P < 0{\cdot}05$ (*) between groups receiving MMI alone and those receiving combined therapy.

Statistical analysis

The baseline characteristics and results among patient groups were compared using the Mann–Whitney *U* test. Comparison of frequencies was analyzed using Fisher's exact probability test. Differences were considered significant at $P < 0{\cdot}05$.

Results

Comparisons of the efficacy of MMI treatment with that of MMI plus KI treatment

Pertinent clinical data are summarized in Table 1. The ratio of sex, values for age, TRAb and goitre size before treatment did not differ among the four groups. Figure 1 shows serial changes in serum FT4 and FT3 in the four groups. After 2 weeks of treatment, FT4 levels rapidly decreased and mean FT4 values were significantly lower ($P < 0{\cdot}01$) in the groups receiving combined therapy (Groups 2 and 4) (Fig. 1a and c) compared with those of the groups receiving MMI alone (Groups 1 and 3). Similarly, serum FT3 levels rapidly decreased after 2 weeks of treatment and mean levels were significantly lower ($P < 0{\cdot}01$ and $P < 0{\cdot}05$) in the groups receiving combined therapy (Groups 2 and 4) (Fig. 1b and d) compared with those of the groups receiving MMI alone (Groups 1 and 3).

The efficacy of treatment in terms of normalization of serum FT4 and FT3 was compared between groups receiving MMI alone and those receiving MMI + KI. Comparison of results between Group 1 (MMI 30 mg) and Group 2 (MMI 30 mg + KI) are shown in Fig. 2a and b. After 2 and 4 weeks of treatment, normal FT4 was observed in 29% and 71%, respectively, of patients in Group 1, and 59% ($P < 0{\cdot}05$) and 78% ($P = 0{\cdot}5839$), respectively,

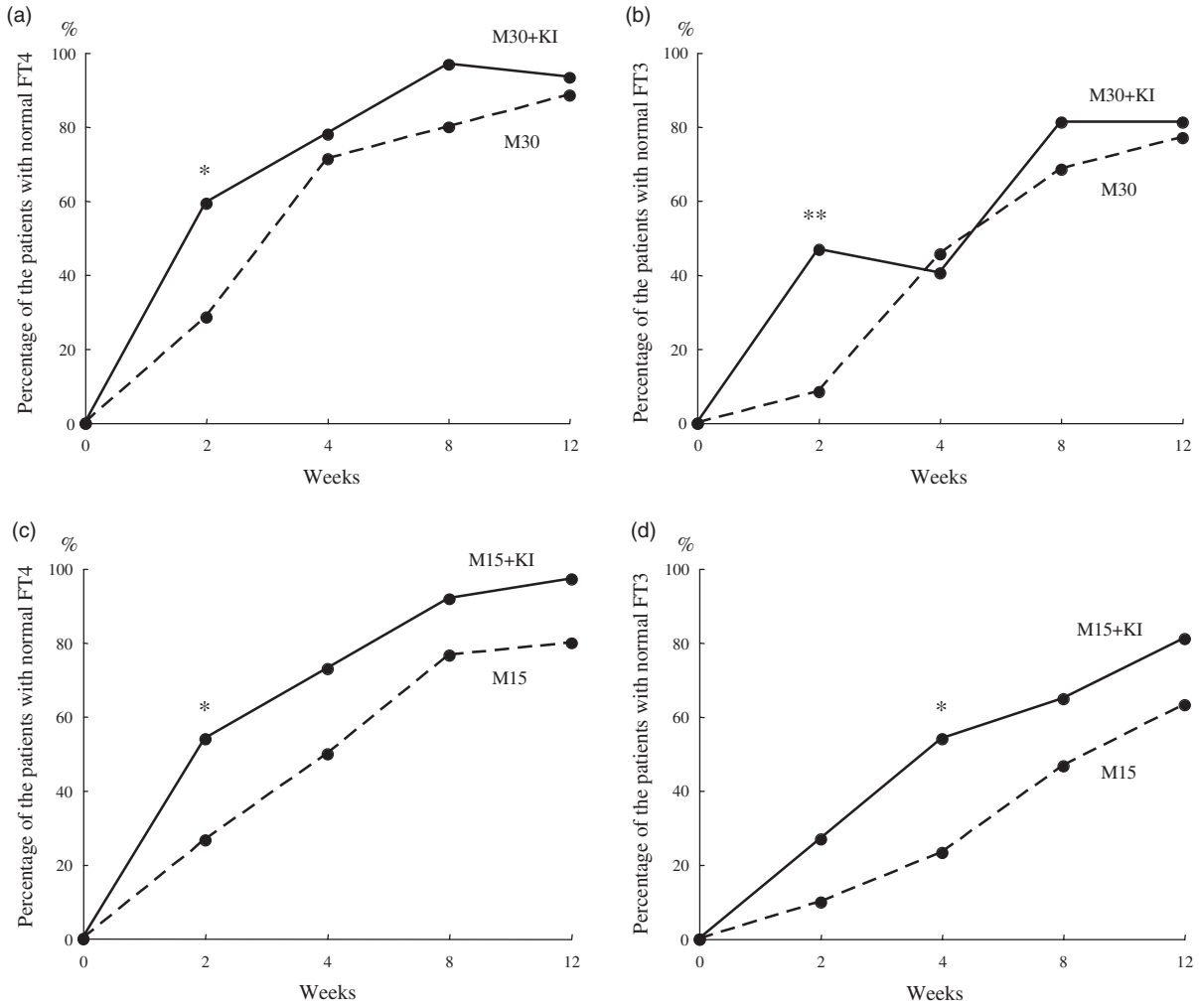

Fig. 2 The efficacy of treatment in terms of the normalization of serum FT4 or FT3 was compared between groups receiving MMI alone (dotted line) and those receiving MMI + KI (solid line). Comparison of results between Group 1 (MMI 30 mg) and Group 2 (MMI 30 mg + KI) are shown in (a) (FT4) and (b) (FT3). Comparison of results between Group 3 (MMI 15 mg) and Group 4 (MMI 15 mg + KI) are shown in (c) (FT4) and (d) (FT3). In Group 2, the percentage of patients demonstrating normal FT3 was increased after 2 weeks of treatment, but then decreased transiently at 4 weeks. FT4 was considered normalized when it decreased to <20·64 pmol/l. FT3 was considered normalized when it decreased to <5·72 pmol/l. Significantly different at $P < 0{\cdot}01$(**) and $P < 0{\cdot}05$(*) between groups receiving MMI alone and those receiving combined therapy.

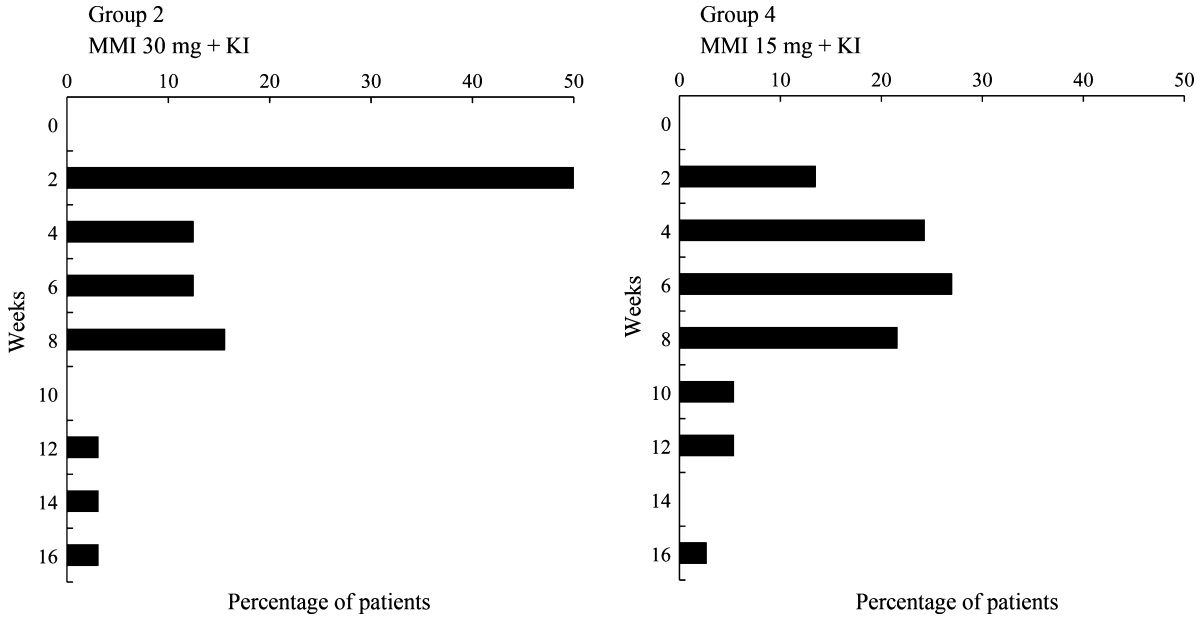

Fig. 3 Comparison of the duration of KI usage between Group 2 (MMI 30 mg + KI) and Group 4 (MMI 15 mg + KI).

of patients in Group 2 (Fig. 2a). Percentages showing normalization of FT4 in Group 3 (MMI 15 mg) and Group 4 (MMI 15 mg + KI) are shown in Fig. 2c. After 2 and 4 weeks of treatment, normal FT4 was observed in 27% and 50%, respectively, of patients in Group 3, and 54% ($P < 0{\cdot}05$) and 73% ($P = 0{\cdot}0758$), respectively, of patients in Group 4. As for normalization of FT3, similar results were obtained (Fig. 2b and d). In Group 2, the percentage of normal FT3 was increased after 2 weeks of treatment but then decreased transiently at 4 weeks, possibly due to the cessation of KI (Fig. 2b).

Duration of KI usage and transient increase of thyroid hormones after cessation of KI

We discontinued KI tablets when patients showed normal FT4. As shown in Fig. 3, 50% of patients could discontinue KI after 2 weeks of treatment in Group 2, but only 14% of patients could do so in Group 4 ($P < 0{\cdot}05$). The mean duration of KI administration was $4{\cdot}9 \pm 3{\cdot}8$ weeks in Group 2 and $6{\cdot}2 \pm 3{\cdot}1$ weeks in Group 4, and the difference between the two groups was significant at $P < 0{\cdot}01$. However, 86% of patients in Group 4 could discontinue KI within 8 weeks. None of the patients showed an increase of thyroid hormones or aggravation of disease during combined treatment with MMI and KI. Furthermore, none of the patients showed any side effects of KI tablets.

After cessation of KI, transient increase of FT4 more than 20·64 pmol/l was observed in 3 (9·4%) and 3 (8·1%) patients in Group 2 (MMI 30 mg + KI) and Group 4 (MMI 15 mg + KI), respectively, but FT4 quickly returned to the normal range under continuing administration of MMI. These transient increases were not related to the initial values of FT4, TRAb or goitre size before treatment or to FT4 levels at the time of KI discontinuation.

Table 2. Relation of four treatment regimens and disease remission during 4- to 5-year observation period

			No. of patients		
Group	Drugs	No. examined	Remission	No remission	Remission rate (%)
1	MMI30 mg	35	12	23	34
2	MMI30 mg + KI	32	14	18	44
3	MMI15 mg	30	10	20	33
4	MMI15 mg + KI	37	19	18	51

Relation of the four treatment regimens and disease remission

As shown in Table 2, the remission rate was higher in the groups receiving KI (Groups 2 and 4) than in those receiving MMI alone (Groups 1 and 3), but these differences were not significant (Group 1 *vs.* Group 2, $P = 0{\cdot}4615$: Group 3 *vs.* Group 4, $P = 0{\cdot}2148$). Statistical analysis was also performed to compare Groups 1 and 3 combined with Groups 2 and 4 combined, but the P value was 0·10 (CI 95%).

Discussion

Iodide has been given to patients with severe thyrotoxicosis because of its ability to acutely block thyroid hormone release.[14] Although almost all patients respond initially, about one-third respond only partially and remain toxic, and another one-third respond initially but relapse after about 6 weeks.[8] At the present time, the use of iodide alone as definitive therapy for thyrotoxicosis has been discarded and iodide is primarily used in conjugation with ATDs to prepare patients for thyroidectomy.[15]

Iodide administration in combination with ATDs has been reported to reduce the efficacy of ATDs *in vitro*.[16–18] Roti *et al.* reported that the combination of ATDs with Lugol's Iodine was no more effective than ATDs alone in restoring serum thyroid hormone concentrations to normal. However, sodium ipodate added to ATDs did reduce serum T3 and control heart rate more rapidly.[7] Martino *et al.* reported that monotherapy of Graves disease with iodide produced only short term control of thyrotoxicosis and that its use impaired the efficacy of subsequent treatment with ATDs.[19]

It is reported that MMI more effectively reduces thyroid hormones in Graves' patients who are living in countries with a moderately low iodine intake, compared with that in those in areas with sufficient dietary iodine intake.[20] Considering this background, in Western countries, iodide has rarely been used in combination with ATDs to reduce thyroid hormone secretion in ordinary patients with Graves' disease and not at all for patients with toxic multinodular goitre, as it is well known that excess iodide aggravates thyrotoxicosis in multinodular goitre.[21]

In this study, however, we clearly observed the rapid reduction of thyroid hormones by combination therapy with MMI and KI and hormone reduction is more effective than with MMI monotherapy. Roti *et al.* administered six drops of saturated solution of KI twice daily (600 mg of KI/day) in Italy.[7] In our study, we used 50 mg of KI/day in Japan, where the general population is well known to consume an iodine-rich diet. For patients, administering a saturated solution of KI or Lugol's solution may be bothersome but we found that compliance with KI tablets was good. Differences in these drug doses and geographic areas may relate to the discrepancy between our results and previous studies. In Japan, Kasai *et al.*[22] used propylthiouracil (PTU) (300 mg/day) combined with small doses of iodide (3 or 6 mg/day) for <3 weeks and they found that combined therapy was much more effective than PTU or iodide alone in the early phase of treating hyperthyroidism, although they did not examine the long term effect. Their data and our results in this study clearly show the effectiveness of combined therapy with ATDs and KI in the early normalization of thyroid hormones.

Although it is well known that use of iodide as monotherapy may result in escape from control of thyrotoxicosis,[23] our study shows that this does not occur when iodide is administered contemporaneously with ATDs. Nor did we observe a reduction in the effectiveness of ATDs when iodide was administered.

In the ATD treatment of patients with Graves' hyperthyroidism, it has been reported that there might be an inverse relationship between the average daily dietary intake of iodine and the remission rate.[24] In this study, however, the remission rate was higher in the group receiving combination therapy than that in the group receiving MMI alone, although the difference did not reach significance. The remission rate after 2–3 years of treatment with ATDs is around 40% in Japan[25] and our study does not indicate an adverse effect of iodide on remission rate.

Guidelines for the treatment of Graves' disease from the Japan Thyroid Association[26] recommend the use of MMI 15 mg/day for mild and moderate Graves' disease, whereas MMI 30 mg/day is recommended for severe cases, as normalization of FT4 is similar between 15 and 30 mg in mild and moderate cases and adverse effects including agranulocytosis[27] are less frequent in patients receiving MMI 15 mg compared with those in patients receiving MMI 30 mg. In combined therapy with MMI 15 mg and KI, normal FT4 was obtained in 73% of patients after 4 weeks of treatment, although the duration of KI usage was slightly longer than that of those receiving MMI 30 mg + KI treatment. If iodine is to be used in combination with ATDs for treatment of thyrotoxicosis due to Graves disease, then our study suggests that 15 mg of methimazole is adequate.

In conclusion, in our patients, combined treatment with MMI and KI more rapidly normalised thyroid hormones than MMI alone in patients with Graves' disease. Although we found no statistical difference in the rate of remission in patients treated with iodide, we feel a larger study with adequate power should be undertaken to examine this important issue.

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