Therapeutic efficacy and limitations of potassium iodide for patients newly diagnosed with Graves’ disease

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Abstract. The efficacy of potassium iodide (KI) for Graves’ disease (GD) has been reported, although few clinical reports have examined the long-term efficacy of treatment. The objective of this study was to investigate the efficacy and limitations of KI treatment for GD. This study enrolled patients newly diagnosed with mild GD, defined as free thyroxine (FT4) <5.0 ng/dL, between July 2014 and June 2016. KI was started at a dose of 50 mg/day, and if FT4 values did not decrease after initiation of treatment, doses were increased to 100 mg/day. Patients for whom thyroid hormone levels could not be controlled with KI at 100 mg/day were regarded as non-responders. Of the 122 patients (13 males, 109 females) included in this study, 71 (58.2%) responded to KI therapy. The remaining 51 patients (41.8%) were non-responders. The median duration required to judge non-responsiveness was 5.9 months. Multiple logistic regression analysis performed on parameters measured at the initial visit indicated FT4 (odds ratio (OR) 2.19, 95% confidence interval (CI) 1.28–3.75; \( p = 0.0007 \)) and male sex (OR 3.58, 95%CI 1.04–12.3; \( p = 0.04 \)) were significantly associated with KI responsiveness. Receiver operating characteristic (ROC) curve analysis of the relationship between FT4 and KI responsiveness indicated an FT4 cut-off of 2.76 ng/dL was optimal for differentiating between responders and non-responders. KI therapy was effective and safe for about 60% of patients with mild GD.

Key words: Potassium iodide, Graves’ disease, Graves’ hyperthyroidism, Wolff-Chaikoff effect

INORGANIC IODIDE is essential for humans, as an integral component of thyroid hormone. Excessive iodine intake is well known to reduce thyroid hormone secretion and production, as excess iodine inhibits iodine organization in the thyroid gland. This phenomenon is known as the Wolff-Chaikoff effect [1-3]. A detailed animal experiment showed that excess iodine reduces the expression of thyroid peroxidase (TPO) mRNA, and expressions of sodium/iodine symporter (NIS) mRNA and protein [4]. These mechanisms could be involved in the decreasing concentrations of thyroid hormone seen under conditions of insufficient iodide. The effect of excess iodine supplementation has been used as a treatment for GD for decades [5], especially during thyroid crisis, in combined use with anti-thyroid drugs (ATDs) for patient with severe hyperthyroidism [6, 7] and as a surgical preparation [8]. However, that effect is not believed to last long, with the loss of effect termed “escape from the Wolff-Chaikoff effect” [4]. Although almost seven decades have passed since ATDs were first used in the treatment of GD [9], potassium iodide (KI) has seen preferential use for patients with GD in Japan who display adverse reactions to ATDs. According to this background, few reports have examined the efficacy of KI treatment [10-12]. We therefore planned the present study to investigate the treatment efficacy and limitations of KI treatment for newly diagnosed GD patients.

Materials and Methods

Subjects

Subjects in this study were patients with newly diagnosed mild GD between 15 and 69 years old, seen by full-time physicians at our institution during the period from July 2014 to June 2016 (Fig. 1). GD was diagnosed based on both hyperthyroidism and positive thyrotropin (TSH) receptor antibody (TRAb) or TSH stimulating antibody (TSAb), or diffuse high uptake of radioactive
iodine. Mild hyperthyroidism was defined as a free thyroxine (FT4) value less than 5.0 ng/dL. Patients who were pregnant or lactating, trying to become pregnant in the near future, or with severe comorbidities (such as ischemic heart disease, heart failure, liver failure, kidney failure or diabetes mellitus) were not considered eligible for the present study. Patients who deviated from the treatment protocol or were lost to follow-up within a month of starting KI were excluded from analysis. A total of 168 patients met the inclusion criteria. All subjects were followed-up every month for the first 3 months, then every two to three months to check thyroid function using the serum concentrations of free triiodothyronine (FT3), FT4 and TSH. Written informed consent was obtained from all subjects prior to enrolment in this prospective study.

Treatment with KI was commenced at a dose of 50 mg/day. If FT4 values did not decrease to the upper limit of normal (1.6 ng/dL) after initiating treatment, the KI dosage was increased to 100 mg/day. On the other hand, when TSH values were elevated to be within the normal range (0.2–4.5 μU/mL), the KI dose was decreased by 10 mg/day. KI was continued at the same dose when TSH values were below the lower limit of normal and FT4 values were within the normal range. The lowest maintenance dose of KI was set as 10 mg every other day. Patients in whom FT4 levels could be controlled to within the normal range with a KI dose >100 mg/day were regarded as non-responders. Medication was stopped when both TSH values had been kept <3.0 IU/L for more than 6 months under a KI dosage of 10 mg every other day. Details of the dosage adjustment for KI are shown in Fig. 2. The observation period was set as three years after starting KI, or until the patient was regarded as a non-responder, whichever occurred first. All study protocols were approved by the Ethics Committee of Ito Hospital.

**Methods**

Serum FT3 concentration was measured using an ECLusys FT3 electrochemiluminescence immunoassay kit (Roche Diagnostics, Basel, Switzerland; reference range, 2.2–4.3 pg/mL). Serum FT4 was measured using an ECLusys FT4 electrochemiluminescence immunoassay kit (Roche Diagnostics; reference range, 0.8–1.6 ng/dL). Thyrotropin was measured using an ECLusys TSH electrochemiluminescence immunoassay kit (Roche Diagnostics; reference range, 0.2–4.5 μU/mL). TRAb values were measured using an ECLusys TRAb electrochemiluminescence immunoassay kit (Roche Diagnostics; normal range, <2.0 IU/L). TSAb was measured using a TSAb radioimmunoassay and bioassay kit (Yamasa, Choshi, Japan; reference range, <120%).

Thyroid volume was estimated by ultrasonographically measuring the length, width, and depth of each lobe of the thyroid gland in millimeters, then calculating the volume according to the following formula: thyroid volume = (0.7365 × right lobe length × width × depth + 0.7412 × left lobe length × width × depth) – 0.55 [6].

**Statistical analysis**

All the collected data were analyzed using JMP version 14.0 software (SAS Institute, Cary, NC). The Wilcoxon
rank-sum test was applied to compare parameters between KI responder and non-responder groups, and the Wilcoxon signed-rank test was used to compare the volumes of the thyroid at the initial visit and a year later. Pearson’s chi-squared test was used to compare the prevalence of KI responders and non-responders. Fisher’s exact test was used to compare parameters when the number of subjects was small. Correlation analyses were performed using multiple logistic regression analysis. ROC curve analysis was used to determine cutoff values for the variables.

**Results**

**Patient characteristics and clinical course**

Of the 168 patients who met the inclusion criteria and did not meet the exclusion criteria, 46 patients were excluded. These exclusions were due to deviation from the treatment protocol in 27 patients (when the condition of the subject was unfavorable, the physician started ATDs for its definitive and accurate effect, without increasing the dose of KI), and loss to follow-up within a month in 19 patients. The remaining 122 patients (13 males, 109 females) were analyzed (Fig. 1). Detailed characteristics of the 122 subjects are shown in Table 1. The median value of TRAb was 4.65 IU/L, although seven of the 122 subjects showed negative results for TRAb. TSAb was measured in 5 of the 7 patients who showed negative results for TRAb, and all 5 patients showed positive results for TSAb. The remaining 2 of 7 patients for whom TSAb was not measured showed positive results for TRAb at 2 and 4 months after initiating KI. The smoking rate of subjects was 61.5% (8 of 13) in males, 13.8% (15 of 109) in females and 18.9% (23 of 122) in total. Smoking rates were significantly higher for male subjects than for female subjects ($p = 0.0003$). All subjects experienced a decrease in thyroid hormone concentrations after initiating KI. The dosage of KI required for controlling thyroid hormone are shown in Table 1. No patients presented with any side effects of KI. The 122 subjects comprised 71 KI responders (58.2%) and 51 patients KI non-responders (41.8%).

**Characteristics of KI responders**

Detailed data for the 71 responders (4 males, 67 females; 58.2%) are shown in Table 1. Among the 71 KI responders, 36 patients (2 males, 34 females; 50.7%) were able to discontinue KI. Median values of FT3, FT4
and TRAb at the time of KI discontinuation were 2.75 pg/mL (range, 2.2–4.0 pg/mL), 1.13 ng/dL (range, 0.88–1.6 ng/dL), and 0.9 IU/L (range, 0.3–29.0 IU/L), respectively. In addition, median concentration of TSH at the time of KI discontinuation was 1.95 μIU/mL (range, 1.0–6.12 μIU/mL). The remaining 35 patients (2 males, 33 females; 49.3%) were unable to discontinue KI, but remained well-controlled on KI therapy. Between the KI discontinued and controlled groups, no significant differences in the parameters of sex, age, serum FT3 and FT4 values, TRAb value or initial thyroid volume were seen, although the observation period was significantly shorter in the KI discontinued group ($p < 0.0001$).

**Characteristics of KI non-responders**

As described above, 51 of the 122 patients (9 males, 42 females; 41.8%) were judged as KI non-responders (Table 1). All 51 patients switched from KI to ATDs after being judged as non-responders, although 5 of the 51 patients developed adverse events of ATDs. Among these 5 patients, 2 patients developed agranulocytosis due to thiamazole (MMI), 1 patient developed liver injury due to propylthiouracil, and 2 patients developed drug eruption attributed to MMI. Four of the 5 patients could not continue ATDs and chose radioactive iodine (RAI) therapy for definitive treatment. Moreover, even though the remaining 46 patients did not develop adverse events, 3 of those 46 patients changed therapies due to difficulties in controlling hyperthyroidism with ATDs, 1 patient underwent surgery and 2 patients received RAI therapy. Median serum concentration of TRAb at the judgement of non-responder status was 9.1 IU/L (range 0.3–40.0 IU/L), significantly higher than that at the time of diagnosis with Graves’ disease ($p < 0.0001$).

**Comparison of baseline parameters between KI responders and non-responders**

Table 1 also shows comparisons of baseline parameters between KI responder and non-responder groups. Age, TRAb value and thyroid volume showed no significant differences between groups, although the ratio of male sex and serum concentrations of FT3 and FT4 were significantly higher in the KI non-responder group. Relationships between parameters at initial visit and KI responsiveness are shown in Table 2. Multiple logistic regression analysis indicated FT3 and FT4 levels and male sex as factors significantly related to KI responsiveness (FT3, per 1-pg/mL increase: odds ratio (OR) 1.11, 95% confidence interval (CI) 1.00–1.23, $p = 0.04$; FT4, per 1-ng/dL increase: OR 2.19, 95% CI 1.28–3.75, $p = 0.002$; male sex: OR 3.59, 95%CI 1.034–12.3, $p = 0.04$).

| Table 1 | Detailed parameters of the 122 patients and comparisons between KI responders and KI non-responders |
|---------|--------------------------------------------------------|
|         | Total, $n = 122$ | Responders, $n = 71$ | Non-responders, $n = 51$ | $p$-value |
| Sex, n (%) | | | | |
| Male | 13 (10.7) | 4 (5.6) | 9 (17.6) | 0.04 |
| Female | 109 (89.3) | 67 (94.4) | 42 (82.3) | |
| Age (years) | | | | |
| Median (range) | 47 (15–69) | 46 (15–68) | 47 (20–69) | 0.38 |
| FT3 (pg/mL) | | | | |
| Median (range) | 8.55 (3.7–19.8) | 7.5 (3.7–19.8) | 9.6 (4.5–17.0) | 0.01 |
| FT4 (ng/dL) | | | | |
| Median (range) | 2.88 (1.32–4.9) | 2.6 (1.32–4.86) | 3.3 (1.75–4.90) | 0.0005 |
| TRAb (IU/L) | | | | |
| Median (range) | 4.65 (0.3–40.0) | 4.9 (0.8–40.0) | 4.6 (0.3–30.3) | 0.77 |
| Thyroid volume* (mL) | | | | |
| Median (range) | 22.1 (9.7–85.5) | 21.9 (10.7–85.5) | 23.8 (9.7–63.7) | 0.08 |
| Observation period (months) | | | | |
| Median (range) | 27.9 (1.6–46.7) | 37.2 (4.5–46.7) | 5.9 (1.57–25.4) | 0.08 |
| Maximum dose of KI required for subjects (n) | | | | |
| 50 mg | 54 | 0 |
| 60–90 mg | 3 | 0 |
| 100 mg | 14 | 51 |

* Initial
Analysis of the ROC curve for the relationship between FT4 value and KI responsiveness revealed a cut-off FT4 value of 2.76 ng/dL as optimal for differentiating between responders and non-responders (area under the ROC curve (AUC) = 0.684) (Fig. 3). Moreover, among those subjects with FT4 values lower than 2.8 ng/dL, 79% were KI responders, although 42% of subjects with FT4 values above 2.8 ng/dL also displayed good response to KI therapy.

Changes to thyroid volume

Changes to thyroid volume were observed in some patients during the treatment period. Thyroid volume was evaluated in 91 subjects at both initial visit and approximately one year after commencing KI (Fig. 4). A significant increase in thyroid volume was observed in the total subject group (p < 0.0001), in KI responders (n = 59; p = 0.0007), and in KI non-responders (n = 32; p = 0.0001). As a baseline parameter, thyroid volume showed no difference between KI responders and non-responders (p = 0.106), although the thyroid volume of subjects one year later was significantly larger in the KI non-responder group (p = 0.0001). Median rate and amount of thyroid volume change in each group were Δ0.152 (+2.6 mL) in total subjects, Δ0.108 (+1.94 mL) in KI responders, and Δ0.315 (+7.32 mL) in KI non-responders, respectively. Even though a significant increase in thyroid volume was observed in all groups, some subjects showed a decrease in thyroid volume. In detail, 14 of the 59 KI responders (23.0%) and 7 of the 32 KI non-responders (21.9%) exhibited a decrease in thyroid volume. Comparing TRAb values between time of diagnosis and last follow-up among these 14 and 7 subjects who showed decreased thyroid volume, no significant differences were seen between KI responders and non-responders groups (p = 0.962 and p = 0.338, respectively). Furthermore, 8 of the 14 KI responders with decreasing thyroid volume were able to be withdrawn from KI.

Discussion

This prospective study showed the efficacy and limitations of KI monotherapy for newly diagnosed, mild GD in Japan. A previous report by Uchida et al. [11] suggested that 85% of mild GD patients could be controlled with KI alone, and Okamura et al. showed that KI was effective for about 60% of patients with GD. Compared to these previous reports [10-12], the present study confirmed that KI therapy is effective for GD in patients with FT4 values <5.0 ng/dL. Differences in treatment strategy and subject enrollment criteria existed between these reports and our study, as subjects in previous studies had also been treated with ATDs as a first-line treatment. ATDs are known to induce morphological changes in thyroid tissue, such as increased cellularity and diminished amounts of colloid [13]. Considering this fact, thyroid tissues from subjects analyzed in previous reports [10-12] were likely to have been affected by ATDs, and such degeneration might have impacted the efficacy of KI. Although, similarities were present between this and previous studies, such as the factors related to KI responsiveness, our study was designed as a prospective study, and all subjects were treated using KI alone, meaning that our study provides more accurate data on the effects of KI.

The immune-activating effects of excess iodine intake reportedly results in the development of autoimmune thyroiditis [14-16]. However, the ways in which long-term use of KI affects the immune system remain uncertain. Moreover, no patients in this study presented with side effects of KI, such as rash or nausea. In terms of
side effects, ATDs are known to sometimes cause life-threatening problems, such as drug-induced liver injury and agranulocytosis. KI monotherapy appears potentially safer as a treatment for patients with GD.

The present study showed a significant difference in KI responsiveness between sexes. The efficacy of medication for GD including KI has limitations, so some patients with GD have to choose alternative methods to treat their disease. One report from the United Kingdom analyzing 536 GD patients treated with ATDs indicated that male patients displayed a significantly higher prevalence of relapse [17]. Similarly, Magri et al. showed in a study of 294 GD patients treated with ATDs that compared with female patients, males had a significantly higher rate of hyperthyroidism relapse and a significantly higher rate of relapse in later years, resulting in poorer prognosis [18]. On the other hand, some reports have described sex as having no relationship to the outcome of treatment with ATDs [19, 20]. In the present study, males displayed a 3.6-fold higher risk of KI non-responsiveness than females. Since subjects in our study were treated with KI alone, with no ATDs, the mechanisms of treatment differed markedly. However, the results showed a similarity between these two approaches, suggesting that KI could represent a third option for female patients with mild GD. Moreover, smoking rates were significantly higher in male subjects than that in female subjects in the present study, which might have affected differences in KI responsiveness between sexes.

Some studies have indicated thyroid enlargement is induced by oral intake of iodine. Namba et al. observed reversible thyroid enlargement in healthy euthyroid volunteers after administration of iodine [21]. Likewise, Yabuta et al. noted that thyroid volume in patients with GD increased after preoperative administration of KI, even with durations less than a month [22]. In the present study, thyroid volume for the total subject group was significantly increased after one year, compared with baseline volume, and thyroid volume changes were larger in the KI non-responder group. However, not all subjects showed increased thyroid volume, with 21 patients (23%) presenting with decreases in thyroid volume. Furthermore, previous reports have indicated initial thyroid volume as one of the risk factors for GD recurrence [17, 19, 20], suggesting that a larger thyroid volume could be associated with higher risk of recurrence. Since no correlation was seen between baseline thyroid volume and KI responsiveness in the present study, this difference might be due to the smaller number of subjects, or to differences in ethnicity. Even so, signifi-

Fig. 4 Changes in thyroid volume over time. Blue line shows patients in whom thyroid volume decreased over time, red line shows patients in whom thyroid volume increased over time, green line shows patients in whom thyroid volume remained the same. A significant increase in thyroid volume was observed in the total subject group ($p < 0.0001$), KI responders ($p = 0.0007$), and KI non-responders ($p = 0.0001$). At baseline, thyroid volume did not differ significantly between KI responders and non-responders ($p = 0.106$), although significant enlargement of the thyroid was evident 1 year later in the KI non-responder group ($p = 0.0001$).
significant enlargement of the thyroid was recognized in the KI non-responder group, suggesting that patients displaying an increase in thyroid volume during the clinical course might have a greater risk of KI non-responder status.

Some limitations to this study need to be considered. The number of male subjects was relatively small in this study, and this bias might have affected the results. Further statistical analysis in a larger cohort is thus warranted to confirm our results. Furthermore, iodine intake in the general population differs between countries, as mentioned earlier, and all previous articles that showed the efficacy of KI were reported from Japan, which is known as an iodine-sufficient country. Notably, baseline iodine intake may affect the efficacy of KI, and this result would thus not be applicable to iodine-insufficient countries.

Conclusion

KI therapy appears to offer an effective and potentially safer therapy for about 60% of female patients with mild GD, and thus could represent a third drug option for these patients.

Disclosure statement

All authors declared no conflicts of interest associated with this manuscript.

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