# Remission After Potassium Iodide Therapy in Patients With Graves' Hyperthyroidism Exhibiting Thionamide-Associated Side Effects

Ken Okamura, Kaori Sato, Megumi Fujikawa, Sachiko Bandai, Hiroshi Ikenoue, and Takanari Kitazono

Department of Medicine and Clinical Science, Graduate School of Medical Sciences, Kyushu University, Higashi-ku, Fukuoka 812-8582, Japan.

**Context:** Thionamides have various side effects.

**Objective:** The effectiveness of potassium iodide (KI) was evaluated in hyperthyroid patients who experienced side effects to thionamides.

**Design and Setting:** An observational study was conducted at an academic medical center.

**Patients:** Among 1388 patients with Graves' hyperthyroidism treated with thionamides, 204 (14.7%) exhibited side effects, and 44 were treated with KI and followed for 17.6 (median; range, 8.6–28.4) years.

**Main Outcome Measures:** The primary endpoint was the initial response to KI, and the secondary endpoint was the long-term prognosis.

**Results:** The conditions of 29 (65.9%) of the 44 patients were well controlled with KI alone (10–400 mg/d) (A group), and 17 (38.6%) patients went into remission after 7.4 (1.9–23.0) years. The conditions of 15 (34.1%) patients were not controlled with KI alone (B group), even at a high dose (100–750 mg/d), but seven patients (15.9%) were controlled with a combination of KI and low-dose thionamides, resulting in remission after 7.2 (2.8–10.8) years. The initial parameters did not predict the response to KI or long-term prognosis. However, remission occurred in 70.8% of the patients treated with less than 200 mg of KI, compared with 35.0% of the patients who required 200 mg or more of KI ($P < .05$).

**Conclusions:** Among hyperthyroid patients with thionamide-associated side effects, KI therapy was effective in two-thirds of cases, and about 40% of the patients experienced remission after KI therapy alone. The chance of remission was small among the patients refractory to KI. **(*J Clin Endocrinol Metab* 99: 3995–4002, 2014)**

The administration of stable iodide to hyperthyroid patients has been known to produce clinical benefit since the era of von Basedow (1840) and Trousseau (1863) (1–5). Although iodide was used in a desultory manner during the 19th and early 20th centuries, this form of therapy received wide acceptance after the astute observations of Neisser (1920), Loewy and Zondek (1921), and Plummer (1923) (1, 4). Plummer utilized 10 drops of Lugol's solution containing 5% $I_2$ and 10% potassium iodide (KI), once or four times a day (approximately 80–320 mg iodine daily) (5). Starting from the 1930s, Thompson et al (2) reported satisfactory results after giving patients approximately 6 mg of iodine daily in 64% of the mild cases and 10% of the severe cases.

However, the medical literature on iodine contains abundant reference to the dangers of giving the substrate

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Abbreviations: $fT_3$, free $T_3$; $fT_4$, free $T_4$; KI, potassium iodide; MMI, methylmercaptoimidazole; NHI, nonhormonal iodine; NR, non-remission; PTU, propylthiouracil; R, remission; RAIU, radioactive iodine uptake; RI, radioactive iodine; TBII, TSH-binding inhibitor Ig; TSAb, thyroid-stimulating antibody; UI, urinary iodine.

to patients with hyperthyroidism. Giving iodine may have brought temporary relief, but the escape from its effects left the patient in worse straits than he had been in before (1). Jod-Basedow or iodine-induced hyperthyroidism was reported, but that was a complication that arose when iodine was given for endemic goiter (6), except a few reports in the nonendemic area (7). After the introduction of thionamide and radioactive iodine (RI) therapy, iodide was not used in the medical management of hyperthyroidism (1).

After the introduction of assays for detecting the serum thyroid hormone and TSH levels, the initial effects of excess iodide (150–456 mg) in lowering the serum $T_4$ level were confirmed in most studies (8–12). Although sustained elevated $T_3$ levels and the occurrence of the escape phenomenon after 2–14 weeks have been reported (8, 9), some patients achieved euthyroidism and maintained normal $T_4$ and $T_3$ levels for several months (8, 9). Those previously treated with RI or surgery are less likely to exhibit escape from the inhibitory effects of iodide (13).

In Japan, thionamide antithyroid drugs (14) are the first-choice therapy for Graves' hyperthyroidism. However, thionamides have notorious side effects including skin eruption, agranulocytosis, and severe liver damage (15). Ablative therapy is recommended in such cases, but some patients are apprehensive about RI or reluctant to undergo surgery. Before 1998, admission to the hospital was mandatory not only for surgery, but also for RI therapy due to restrictions associated with government rules in Japan. In the present study, we evaluated the efficacy of KI in patients who exhibited side effects to thionamides.

## Patients and Methods

Between 1981 and 2001, 1388 patients with Graves' hyperthyroidism visited our hospital and were treated with either methylmercaptoimidazole (MMI; 1350 cases) or propylthiouracil (PTU; 38 cases). Graves' hyperthyroidism was diagnosed in patients with an elevated serum free $T_4$ ($fT_4$) level and suppressed serum TSH level, when thyroidal radioactive iodine uptake (RAIU) was high, or either TSH-binding inhibitor Ig (TBII) or thyroid-stimulating antibodies (TSAbs) were positive. Functioning thyroid nodules were not included. A total of 204 patients (14.7%) exhibited signs and symptoms suggesting side effects (MMI, 191 cases; PTU, 13 cases), such as skin eruption, leukocytopenia, liver dysfunction, or others. The drug was changed to another thionamide, or the dose was reduced, and an antihistamine drug was administered to the patients with urticaria. With this continued thionamide therapy, 103 patients were treated. Thirty-six patients were treated with RI or surgery, and 21 patients were lost to follow-up. A total of 44 patients (seven males, 37 females; ages, 18–73 y) preferred KI therapy over RI or surgery. None of the patients showed serious complications, such as thyroid crisis or severe eye changes.

The thionamide drugs were discontinued, and KI (13–100 mg) was administered. KI contains approximately 76.5% of iodide. Before 1996, KI powder or 13-mg KI tablets containing 10 mg of iodide (KI, 132 g; Avicel PH102, 1338 g; lactose extra fine crystalline, 400 g; powdered gentian, 120 g; and magnesium stearate, 10 g, to make 10 000 tablets) was prescribed. In April, 1996, 50-mg KI pills containing 38.25 mg of iodide became commercially available (Tanagen Pharmaceutical Co. Ltd, Shiraimatsu Pharmaceutical Co. Ltd, or Nichi-Iko Pharmaceutical Co. Ltd). In this study, the dose is expressed as the dose of KI for convenience.

Before 1990, a small amount of KI (13–39 mg) was administered. However, it became apparent that some patients required more KI, and the initial dose was increased to 39–65 mg in 1990, and then to 100 mg after 1996. The dose of KI was increased to 200–500 mg when euthyroidism was not achieved. Escape from the KI effect was suggested when the serum $fT_4$ and/or free $T_3$ ($fT_3$) level again became elevated while taking KI. If the patient remained euthyroid for 2 years with KI alone, the initial response to KI was considered to be good (A group). If the response was poor and the serum $fT_4$ and/or $fT_3$ levels remained elevated, RI therapy was again recommended (B group). If the patient insisted on receiving antithyroid drug therapy, low-dose thionamide (5–10 mg of MMI or 50–150 mg of PTU) was carefully added to 100 mg of KI, excluding patients with a history of agranulocytosis. After the patient achieved a euthyroid status, the thionamide drug was carefully discontinued, and the patient was treated with only KI for years during follow-up. After the disappearance of thyroid stimulation indices, including positive TBII or TSAb and an enlarged goiter (16), patients were asked whether they wished to stop the drug or continue the KI therapy. If patients remained euthyroid for more than 2 years after stopping the drug, they were considered to have entered remission (R group). Otherwise, the patients were classified into the non-remission group (NR group). The long-term prognosis was compared with that of similarly treated patients who received thionamide after showing minor side effects.

The serum total $T_3$, total $T_4$, $fT_3$, $fT_4$, TSH, and TBII levels, autoantibodies to thyroglobulin and thyroid microsomal antigen, and positivity of TSAb were measured as previously reported (16–18). The serum and urinary total iodine levels and urinary creatinine levels were measured as previously reported (18) in randomly selected patients. Measurement of the iodine level was performed according to the Inductively Coupled Plasma-Mass Spectrometry method starting in 1998 (19). The estimated thyroid weight and 5-hour RAIU were measured as previously reported (17).

### Statistical analysis

Continuous data are presented as the mean ± SD or median (range), as appropriate for each variable. Comparisons were made using Fisher's exact or $\chi^2$ test between categories, and using a multivariate logistic regression analysis, the Mann-Whitney *U* test, and paired sample Wilcoxon signed-rank test between continuous variables. Correlations between continuous numerical variables were assessed using Spearman's rank correlation coefficients. The lengths of time required for TBII to disappear, the goiter to shrink, or the patient to achieve remission were compared using the log-rank test and Cox proportional-hazards model. The analyses were performed using the JMP 10 software program (SAS Institute, Inc). A *P* value below .05 was considered to be statistically significant.

**Table 1.** Clinical Data of Hyperthyroid Patients Treated With KI (Initial Response)

| | A Group | B Group | *P* Value |
|---|---|---|---|
| Initial response to KI | Good | Poor | |
| Before treatment | | | .6460 |
| n | 29/44 (65.9%) | 15/44 (34.1%) | |
| No. of males:females | 3:26 | 4:11 | .4568 |
| Age, y | 41 (20–73) | 42 (18–69) | .7400 |
| Antithyroglobulin antibody (+) | 14/29 | 6/15 | .9954 |
| Antithyroid microsomal antibody (+) | 26/29 | 11/15 | .1381 |
| $fT_4$, ng/dL | 4.5 ± 3.2 | 5.4 ± 3.0 | .5260 |
| Estimated thyroid weight, g | 29 (8–104) | 25 (15–80) | .7016 |
| RAIU, %/5 h | 54.0 (17.1–84.2) | 64.5 (26.1–81.3) | .6418 |
| TBII, % | 31.8 (3.5–85.2) | 43.2 (8.7–80.8) | .5673 |
| TSAb, % | 144 (42–1319) | 211 (85–594) | .9565 |
| Dose of KI during the clinical course | | | |
| Initial dose of KI | | | .2357 |
| <50 mg | 12 | 3 | |
| 50–99 mg | 7 | 3 | |
| 100 mg | 10 | 9 | |
| Maximum dose of KI | | | .0004 |
| <50 mg | 6 | 0 | |
| 50–99 mg | 4 | 2 | |
| 100–199 mg | 10 | 2 | |
| 200–399 mg | 9 | 3 | |
| 400–800 mg | 0 | 8 | |
| Long-term prognosis | | | |
| R group | A-R, 17/29 (58.6%) | B-R, 7/15 (46.7%) | .5316 |
| Drug withdrawn, y | 7.4 (1.9–23.0) (n = 17) | 7.2 (2.8–10.8) (n = 7) | .8489 |
| NR group | A-NR, 12/29 (41.4%) | B-NR, 8/15 (53.3%) | |
| Still on drug | 6/29 (11.5–20.0 y) | 0/15 | |
| $^{131}$I or Surgery, n | 6/29 | 8/15 | .0420 |
| $^{131}$I or Surgery, y | 5.8 (2.3–16.9) (n = 6) | 0.7 (0.2–1.8) (n = 8) | .0024 |
| KI-induced hypothyroidism | 5/29 (17.2%) | | |
| Follow-up interval, y | 17.5 (8.6–28.4) | 15.6 (8.5–24.1) | .2434 |

Values are presented as means ± SD or median (range).

The study was approved by the Ethics Committee of Kyushu University.

## Results

### Initial response and prognosis (Table 1)

After KI therapy, 29 of the 44 patients became euthyroid within 8–329 days (median, 35 d) (good response group, A group). Eighteen patients became euthyroid within 2 months, but it took more than 6 months for five patients in whom the serum $fT_3$ level remained high (5.3–8.1 pg/mL), despite almost normal $fT_4$ levels (0.7–1.7 ng/dL). On the other hand, 15 patients showed poor response to KI therapy (poor response group, B group). The serum $fT_4$ and/or $fT_3$ level remained high in four patients, and escape was suggested in 11 patients after 32–609 (median, 147) days when the serum $fT_4$ level was 1.5–4.9 ng/dL and the $fT_3$ level was 5.3–13.3 pg/mL. In two patients, escape occurred when the KI dose was reduced from 20 to 10 mg or from 60 to 20 mg, respectively.

There were no significant differences in the initial parameters obtained before treatment between the A and B groups (Table 1). However, the maximum dose of KI was significantly higher in the B group.

As to the long-term prognosis in the A group, 17 of the 29 patients (A-R group) eventually went into remission after 7.4 (1.9–23.0) years of KI therapy, with a significant decrease in the TBII activity and estimated thyroid weight, as shown in Figure 1. These patients remained euthyroid for 10.6 (3.6–21.2) years without the drug.

Remission was not achieved in 12 of the 29 patients in the A group (A-NR group). Six of the patients remained euthyroid for 19.5 (11.5–20.0) years with continued KI therapy. The remaining six patients chose RI (n = 5) or surgery (n = 1), although they remained euthyroid for 5.8 (2.3–16.9) years on KI therapy. In two patients, relapse of thyrotoxicosis occurred when the KI therapy was stopped after 6 and 17 years, respectively. Four other patients preferred ablative therapy before marriage or for other reasons. TBII remained positive in five patients, and the estimated thyroid weight increased in one patient in the A-NR group (Figure 1).

In the B group, seven of the 15 patients became euthyroid with careful combined therapy of KI and a small

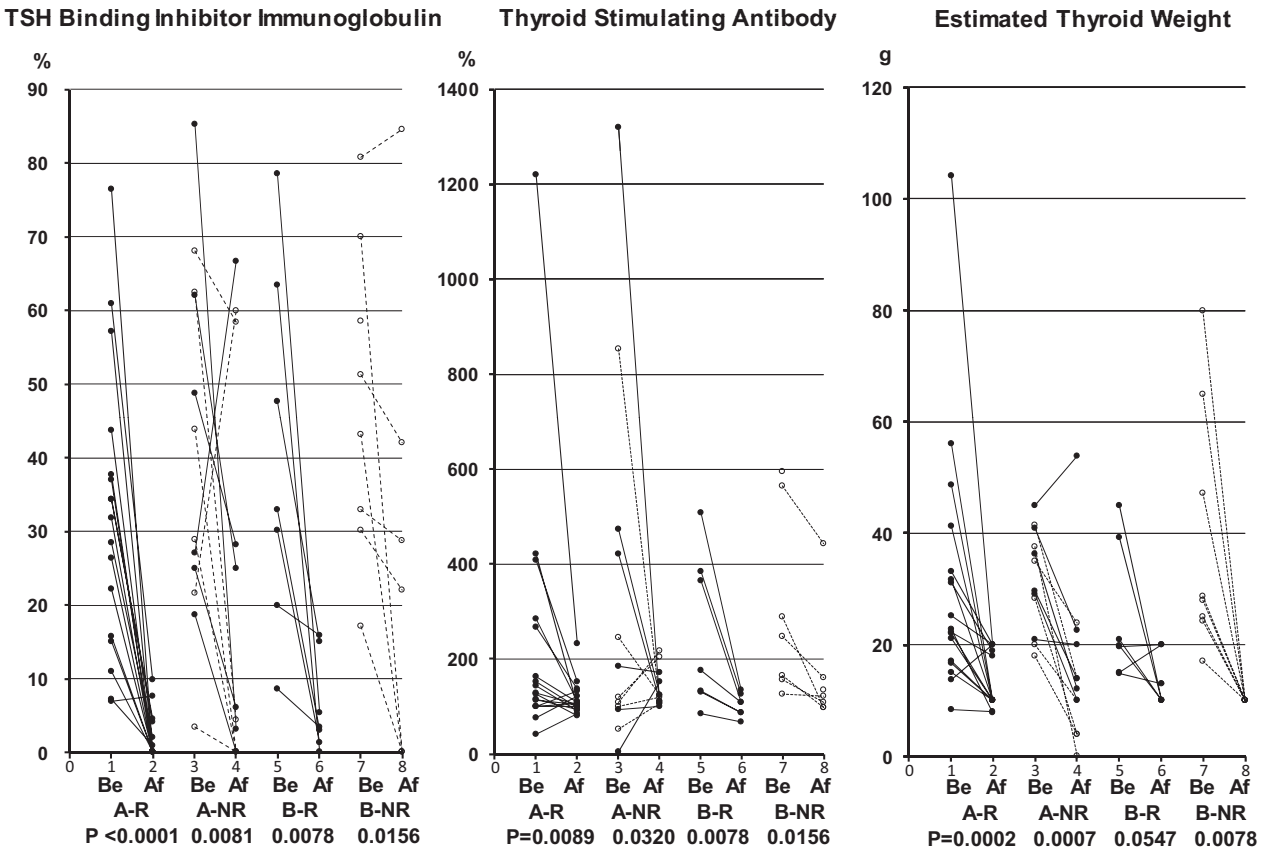


**Figure 1.** Changes in TBII activity, TSAb activity, and estimated thyroid weight before (Be) and after (Af) long-term KI therapy in patients with Graves' hyperthyroidism. A-R (good response with remission), Treated with only KI resulting in remission. A-NR (good response without remission), Initially controlled with only KI. Six patients required continued KI therapy and six other patients (dotted line) later chose RI therapy or surgery. B-R (poor control with remission), Controlled with KI and low-dose thionamide during the initial 2- to 3-year period, followed by KI therapy alone and the attainment of remission. B-NR (poor control requiring ablative therapy), Poorly controlled with KI therapy and treated with RI or surgery (dotted line). The TBII activity and estimated thyroid weight significantly decreased from 43.2 (median; range, 6.9–76.4)% to 2.3 (0.1–7.7)% and from 28.3 (8.4–104) g to 10 (8–20) g, respectively, in the A-R group. The serum TBII levels were determined using radioreceptor assay kits obtained from Baxter Health Care Co. LTD (normal range, <15%) (14, 16, 17). Starting in 2004, the TBII levels were measured using a second-generation TBII assay with the human recombinant TSH receptor (normal, <1 IU/L; DYNOtest TRAb human kit, Yamasa Corp), and the results were expressed as the percentage inhibitory activity. Positivity of TSAb was determined using cultured porcine thyroid cells (normal range, <150%) (16, 17).

amount of thionamides for 1–3 years. No side effects were observed with this small dose of thionamides, and the patients have since remained euthyroid with only KI. They finally stopped taking KI after 7.2 (2.8–10.8) years and remained in remission for 10.7 (4.0–16.5) years thereafter (B-R group). A dramatic decrease in the TBII and TSAb levels and estimated thyroid weight was observed in the B-R group (Figure 1).

Eight patients in the B group were resistant to KI therapy (B-NR group). These patients were successfully treated with RI (n = 7) or surgery (n = 1) within 2 years. In the seven RI-treated patients, the RAIU after 1–2 weeks of KI withdrawal was more than 50% (51.3–76.5%) in six patients and 16.5% in one patient. Five patients became hypothyroid, requiring lifelong replacement therapy, and three other patients remained almost euthyroid for more than 10 years. TBII remained positive in four patients, despite the decrease in the estimated thyroid weight (Figure 1).

The relationship between the initial response to KI and the long-term prognosis was evaluated in Table 2. There were no significant differences between the R group and the NR group, not only in the initial parameters, but also in the initial response pattern, except for the slight difference in the initial TSAb level. However, the maximum dose of KI was significantly higher in the NR group.

## Side effects

None of the patients showed any signs of sialadenitis, hematological abnormalities, liver dysfunction, or skin eruptions. Neither exacerbation of toxicosis nor ophthalmopathy, an increase in the size of the thyroid, or complication of papillary carcinoma was observed after the initiation of KI therapy. A transient increase in the TBII titer (20) was observed in three patients in the A-R group and five patients in the B-R group. Five patients in the A group (three in the A-R group, and two in the A-NR group) became hypothyroid while taking 20–200 mg of KI. The

**Table 2.** Clinical Data of the Hyperthyroid Patients Treated With KI (Long-term Prognosis)

| Long-term Prognosis | R | NR (RI/Ope/Drug) | *P* Value |
|---|---|---|---|
| Before treatment | | | .3237 |
| n | 24/44 (54.5%) | 20/44 (45.5%) | |
| No. of males:females | 4:20 | 3:17 | .5753 |
| Age, y | 38 (20–73) | 46 (18–69) | .9470 |
| Antithyroglobulin antibody (+) | 11/24 | 9/20 | .4933 |
| Antithyroid microsomal antibody (+) | 21/24 | 16/20 | .1512 |
| $fT_4$, ng/dL | 4.5 ± 3.5 | 5.1 ± 2.7 | .2937 |
| Estimated thyroid weight, g | 22 (8–104) | 29 (17–80) | .6487 |
| RAIU, %/5 h | 54.0 (17.1–84.2) | 62.7 (20.9–81.3) | .6324 |
| TBII, % | 32.4 (6.9–78.6) | 43.6 (3.5–85.2) | .5628 |
| TSAb, % | 138 (42–1220) | 245 (52–1319) | .0335 |
| Initial good response to KI | 17/24 (70.8%) | 12/20 (60.0%) | .5316 |
| Follow-up interval, y | 15.7 (8.5–28.4) | 16.8 (8.6–19.8) | .3280 |
| Maximum dose of KI during the clinical course | | | .0324 |
| <199 mg | 17 (70.8%) | 7 (35.0%) | |
| 200–800 mg | 7 (29.1%) | 13 (65.0%) | |

Values are presented as means ± SD or median (range). Patients who failed to achieve remission were classified into the NR group, including those who were treated with RI therapy, surgery (Ope), or continued administration of the drug.

patients were successfully treated with combined therapy of KI and synthetic L-thyroxine (50–75 μg), and all drugs were withdrawn without relapse in the A-R group.

### Urinary iodine (UI) and serum nonhormonal iodine (NHI) levels (Figure 2)

There was a good correlation between the estimated iodine intake and either the UI excretion or the serum NHI level. Although the serum NHI levels were extremely high—exceeding 2.5 μM, the estimated threshold for the Wolff-Chaikoff effect, as suggested in a rat experiment (21, 22)—most of the iodine that did not enter the thyroid was rapidly excreted into the urine. Adherence to drug treatment was easily assessed, as shown in case 1 (see Fig. 2 legend).

### Long-term prognosis of the patients treated with thionamide

Among 103 patients who were continuously treated with thionamides even after showing adverse events, 84 patients were followed for more than 5 years. Forty-two (50%) of the patients went into remission with a negative TBII titer. After remission, the estimated thyroid weight significantly decreased from a median of 28 (range, 10–75) g to 10 (10–28) g ($P < .001$). The median and range of time required for 1) the first disappearance of TBII; 2) goiter shrinkage (<20 g); or 3) remission, in the thionamide- and KI-treated (Table 2) R group were as follows: 1) 484 (0–9269; n = 33) vs 486 (0–5328; n = 24) days ($P = .4571$); 2) 2235 (0–11 705; n = 39) vs 2422 (0–6263; n = 23) days ($P = .3421$); and 3) 2646 (370–12 624; n = 42) vs 2671 (706–8404; n = 24) days ($P = .3623$), respectively. There were no significant differences according to the log-rank test. The Cox proportional-hazards model suggested that sex, age, RAIU, the serum $fT_4$ or TBII level, thyroid weight, and medication had no significant relationship with the time required for remission ($P = .7964$).

## Discussion

It is ironic that the mechanisms for the inhibitory effect of excess iodide on the thyroid gland were elucidated after iodide use had become less common for the medical treatment of hyperthyroidism, except for preoperative preparation or in thyrotoxic crisis. In 1948, Wolff and Chaikoff (21) reported that organic binding of $I^-$ in the rat thyroid was blocked when the plasma $I^-$ concentration reached a critically high threshold (200–350 μg/L or 1.6–2.8 μM) when the rats weighing 200 g were injected 50–500 μg $I^-$, corresponding to 25–250 mg $I^-$/100 kg or 32.7–327 mg KI/100 kg. Using fresh rat thyroid lobes yielding an excellent amount of iodothyronines in vitro, inhibitory effects on $T_3$ or $T_4$ synthesis became apparent when the iodide concentration was over 2.5 μM (22). This phenomenon, known as the acute Wolff-Chaikoff effect suggesting "Too much is as bad as too little," is likely due to the generation of organic iodocompounds, such as α-iodohexadecanal, which may be involved in autoregulatory processes in the thyroid (23). However, the inhibitory effects were shown to be transient due to a decrease in $I^-$ transport induced by a decreased $Na^+/I^-$ symporter activity (24).

Inhibition of organification of iodide might partially explain the clinical effect of excess iodide on Graves' hyperthyroidism (25, 26). However, the effect of iodide on the decrease of serum thyroid hormone levels in Graves'

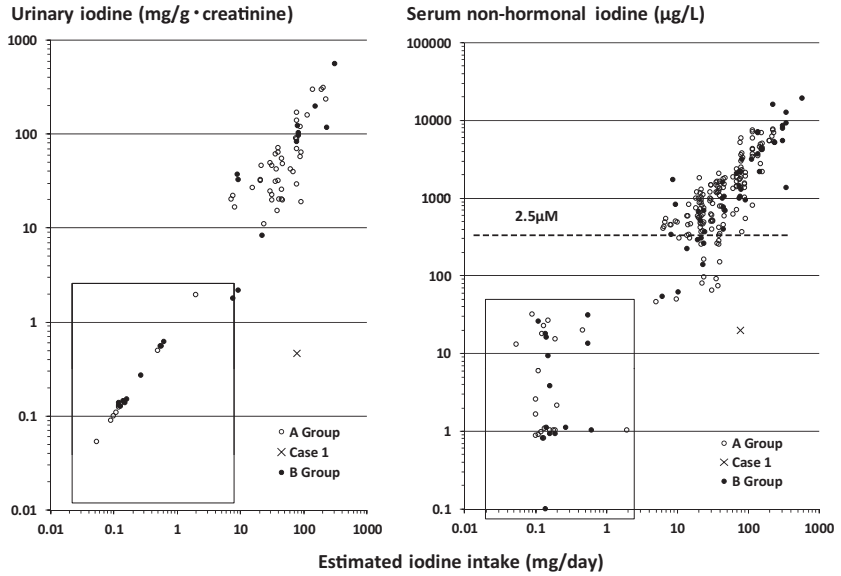


**Figure 2.** UI excretion and the serum NHI levels during different doses of KI therapy depending on the response to the initial KI therapy. Open circle (A group), good response group; closed circle (B group), poor response group. The patient in case 1 (A group) confessed that she had not taken KI before the test, and her data were excluded from the analysis. The estimated iodine intake (EII) from KI therapy (0.765 × KI dose) is shown in abscissa. Before KI therapy, the EII was determined according to the urinary level of excreted iodine, as shown in the rectangle insets. The correlation between iodine intake and the urinary iodine level was r = 0.8878 (UI = 1.32 × EII − 8.0) in the A group and r = 0.9019 (UI = 1.34 × EII − 3.0) in the B group. The correlation between iodine intake and the serum NHI level was r = 0.8685 (NHI = 29.22 × EII − 18.8) in the A group and r = 0.8683 (NHI = 28.48 × EII − 72.3) in the B group. The threshold for the Wolff-Chaikoff effect (2.5 $\mu$M), suggested by the results of a rat experiment (21, 22), is indicated by the dotted line. The serum and urinary total iodine levels and urinary creatinine levels were measured using a Technicon Autoanalyzer, according to the ceric-arsenite method and the Yaffe method, respectively (18). Measurement of the iodine level was performed according to the Inductively Coupled Plasma-Mass Spectrometry method starting in 1998 (19). The correlation between these methods was very good, and the data were analyzed together. Samples containing a high concentration of iodine were analyzed after dilution with 0.02% ammonia with excellent linearity (r = 0.9994). The serum NHI levels were calculated by subtracting the amount of iodine contained in serum $T_3$ and $T_4$ from the total iodine level (18). The mean serum NHI level obtained from 36 euthyroid controls without excess iodide ingestion was 22 ± 14 $\mu$g/L.

hyperthyroidism occurs earlier than that of thionamide (1, 27). It was suggested that, unlike thionamides, excess iodide appears to influence almost all important aspects of iodine metabolism by thyroid gland, including not only iodide organification but also cAMP formation, thyroid growth, vascularity, iodide transport, coupling, and secretion; the last is the more rapid and prominent action in thyrotoxic patients (27, 28). Moreover, necrosis of human thyroid epithelial cells was induced in the presence of more than 10 $\mu$M NaI (29).

It has not been clear why the escape from the effect of excess iodide is often observed in untreated Graves' hyperthyroidism despite the increased iodide uptake (25, 26), whereas the iodide-induced hypothyroidism is common in chronic thyroiditis (30–32) and irradiated or operated patients with Graves' hyperthyroidism (13).

Our results showed that some of the patients with Graves' hyperthyroidism were also susceptible to excess iodide, and iodide therapy alone was effective in 66% of the patients who exhibited side effects to thionamide drugs in Japan after an increase in the dose of KI up to more than 100 mg daily. It is interesting that a decrease in the TBII activity and goiter shrinkage resulting in remission were observed in 17 (38.6%) of the 44 patients after 5–23 years of iodide therapy alone. Whether thionamide drugs have immunosuppressive effects is a controversial issue (33). Our results, together with the findings of a report of a decrease in TBII after perchlorate therapy (34), are discordant with the concept of direct immunosuppressive effects of thionamide drugs.

Iodide therapy alone was not effective in 15 patients in the B group. However, seven patients became euthyroid by adding small doses of thionamide without side effects for a few years and then were kept euthyroid with only KI, resulting in remission. The effect of iodide on the inhibitory effect of thionamides on thyroid peroxidase activity is very complicated (28). The inactivation of thyroid peroxidase by thionamide can be prevented by increasing the iodide concentration (28). However, our clinical study suggested that the effects of thionamides and excess iodide are additive when a large amount of iodide required for the Wolff-Chaikoff effect is administered concomitantly. Seven other patients in the B group were successfully treated with RI as usual. After the withdrawal of KI and iodide restriction, most of the iodide administered was excreted into urine within a few days, suggesting that the KI therapy did not interfere with the efficacy of RI therapy.

Even in the iodide-responsive groups, the required dose of KI varied among the patients (Tables 1 and 2). Although it was shown that iodine-deficient animals were very sensitive to the Wolff-Chaikoff effect (35), the mechanisms underlying the differences in sensitivity to excess iodide in iodine-sufficient areas are unknown (25). Considering the estimated thyroidal and total body iodine content of 10 or 15 mg, respectively (36), a large quantity of iodide is necessary to maintain a sufficient intrathyroidal iodine content to suppress the thyroid function, possibly via passive $I^-$ transport.

The initial parameters did not predict the initial response to KI or the long-term prognosis (Tables 1 and 2).

This was unexpected because previous reports suggested that the candidates for iodide therapy were those with small goiters and mild hyperthyroidism (2). Further studies are required to determine ways to predict the response of the patients to KI therapy. However, remission was observed in 70.8% of the patients whose condition was controlled with less than 200 mg of KI, compared with only 35.0% of the patients who required 200 mg or more of KI, suggesting that the chance of remission is small in patients refractory to KI.

In the present study, remission was observed in 54.5% of the patients in the KI-treated group (Table 2) and 50.0% of the patients in the thionamide-treated group. There were no significant differences in the time required for remission between the KI and thionamide groups. Lippe et al (37) reported a 25% remission rate every 2 years, regardless of the duration of previous therapy in hyperthyroid children treated with long-term medical therapy. The duration rather than the dose or mode of drug treatment may be the important factor associated with the likelihood of remission. It is better to hold the disease in check with the administration of safer and cheaper drugs, such as excess iodide (¥5.6 [US $0.054] per 50 mg KI tablet compared with ¥9.6 [US $0.093] per 5 mg MMI or 50 mg PTU tablet in Japan), if the patients are apprehensive about RI and responsive to KI. The possibility of remission during iodide therapy is important with respect to selecting therapeutic options for the treatment of mild Graves' hyperthyroidism when the patients exhibit side effects to thionamide, including whether to administer single RI once, in the expectation of a physiological effect, or continue to patiently prescribe inorganic iodide for a long period, in the expectation of a sustained chemical effect with the hope of remission.

The advantage of KI therapy is that its effects are reversible without serious side effects, such as leukocytopenia or liver damage. The induction of hypothyroidism (13, 18, 30–32) or a transient increase in the TBII activity (20) may reflect iodide-induced morphological (29), chemical (32), or immunological (31) perturbation within the thyroid. Because reducing the KI dose might induce the exacerbation of thyrotoxicosis in Graves' hyperthyroidism, the patients were treated with combination therapy comprising KI and synthetic L-thyroxine. We did not find any evidence that excess iodide affected the organs without $Na^+/I^-$ symporter, but further studies are required to evaluate the safety of chronic KI therapy.

There is speculation that a decreased quantity of iodide ions in thyroid cells is a direct stimulus of the cell activity (38). Thyroid cells in diffuse toxic goiters may behave as if they are iodine-deficient when in fact they are not. Ingbar (38) proposed the hypothesis of autoregulation of the thyroid, which suggests that thyroid manifestations of Graves' disease may reflect, at least in part, a gland that has lost the ability to sense its own iodine content and hence activate the autoregulatory mechanisms that modulate the thyroid function and growth—a so-called resetting of the thyroid "iodostat." The present study suggests that pharmacological doses of iodide can reverse many of the functional, anatomical (likely via involution) (39), and immunological abnormalities of diffuse toxic goiters after a long clinical course when thyroid hyperplasia is mild or reversible, resulting in a state similar to spontaneous resolution.

It must be stressed that, if the patients preferred KI therapy after showing side effects to thionamide, continuous administration of a large amount of KI was necessary until remission, and that prompt re-evaluation of the treatment was required when escape occurred or thyrotoxicosis remained for more than 3 months requiring more than 200 mg KI.

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Address all correspondence and requests for reprints to: Dr Ken Okamura, Department of Medicine and Clinical Science (Second Department of Internal Medicine), Graduate School of Medicine, Kyushu-University, Maidashi 3-1-1, Higashiku, Fukuoka 812-8582, Japan. E-mail: okamurak@intmed2.med.kyushu-u.ac.jp.

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