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Two-day Thionamide Withdrawal prior to Radioiodine Uptake Sufficiently Increases Uptake and does not Exacerbate Hyperthyroidism Compared to 7-day Withdrawal in Graves' Disease

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Abstract. The appropriate period of antithyroid drug (ATD) discontinuation before radioiodine therapy is the most critical problem in Graves' disease patients under going treatment with ATD. To determine the optimal period that does not alter the outcome of radioiodine therapy or exacerbate hyperthyroidism, we compared serum FT4 levels at radioiodine uptake (RAIU) and therapy outcomes between a 2-day withdrawal group and 7-day withdrawal group. We prospectively recruited 43 patients for the 2-day withdrawal protocol and retrospectively reviewed 49 patients treated with radioiodine following the protocol of 7-day withdrawal. There was no significant difference in RAIU between the 2 groups. The mean serum FT4 level measured on the first day of 24-h RAIU of the 7-day group was significantly higher than that in the 2-day group. There were no significant differences in the outcomes at each point (6 months, 1 year, and 2 years after therapy) between the 2 groups. Our results indicated that withdrawal of ATD for 2 days is superior to 7 days in that 2 days discontinuation did not exacerbate hyperthyroidism. In order to prevent serum thyroid hormone increase after ATD withdrawal and radioiodine therapy, a 2-day ATD withdrawal period before radioiodine therapy may be useful for high-risk patients such as the elderly and patients with cardiac complications. We believe that the 2-day ATD withdrawal method may be useful for patients undergoing treatment with ATD who are to undergo radioiodine therapy.

Key words: Radioiodine therapy, Anti-thyroid drug, Graves' disease, RAIU

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RADIOIODINE therapy is an important therapeutic option for Graves' disease. Several reports have suggested that most patients with Graves' disease do not require antithyroid drug (ATD) pretreatment before radioiodine therapy [1–3]. However, pretreatment is necessary in high-risk patients such as the elderly, patients with severe hyperthyroidism, and those with cardiac complications [4, 5]. Moreover, radioiodine therapy is mainly employed in patients with Graves' disease who do not achieve remission by ATD treatment in some countries [6]. In those cases, most patients receive ATD pretreatment prior to radioiodine therapy, and the issue of the appropriate period of ATD discontinuation before radioiodine therapy is the most critical problem.

Many treatment protocols concerning ATD withdrawal periods before radioiodine therapy have been reported [7–14]. Shorter periods may decrease radioiodine uptake (RAIU) and the success rate of therapy. Longer periods may exacerbate hyperthyroidism and decrease the QOL of patients. Our protocol has traditionally involved a 7-day ATD withdrawal period prior to RAIU and radioiodine therapy. Since we sometimes encountered patients who developed thyrotoxicosis due to ATD discontinuation in our protocol, we tenta-

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tively tried 2-day ATD withdrawal prior to RAIU in several patients. Although the results were satisfactory, the outcome of radioiodine therapy was unknown. To examine the effectiveness of 2-day ATD withdrawal before RAIU and radioiodine therapy, we prospectively investigated the RAIU, serum free thyroxine at uptake, and outcome of therapy in 2-day ATD withdrawal patients. The parameters were compared to those in 7-day withdrawal patients retrospectively.

Subjects and Methods

Subjects

We prospectively recruited 43 patients with Graves' disease for 2-day ATD withdrawal before RAIU and radioiodine therapy in 2000. We retrospectively reviewed patients who were treated with radioiodine following the protocol of 7-day ATD withdrawal in 1996, and selected 49 patients whose thyroid volumes were similar to those of the 2-day withdrawal group as a control, because the difference of thyroid volumes may affect the results. We excluded the patients with large goiter that exceeded 150 g. Graves' hyperthyroidism was diagnosed on the basis of diffuse goiter, thyrotoxicosis, elevated 24-h RAIU, and positive anti-TSH receptor antibodies. All patients were treated with ATD for at least 6 months. Thirty-five patients in the 2-day group and 46 patients in the 7-day group were treated with methimazole and the remainder were treated with propylthiouracil. Most of the patients were treated with ATD during long term and regarded as non-remission cases in both groups. Patients were excluded for overt hyperthyroidism and overt hypothyroidism just before ATD withdrawal. There were no significant differences in thyroid volume, total dose of radioiodine/thyroid weight, duration of the disease, mean ages, and gender between the 2 groups (Table 1).

Treatment

A self-managed low iodine diet was started 7 days before RAIU and stopped 4 days after radioiodine administration in both groups. Radioiodine was administered from 2 to 7 days after RAIU. The serum free thyroxine concentration was measured on the first day of 24-h RAIU, and thyroid weight was estimated by ultrasound on the same day. Patients received a dose of radioiodine on the day of treatment according to the following formula: 80 to 120 μCi/g of estimated thyroid weight/24-h RAIU. ATD was restarted 4 days after radioiodine treatment. Beta-blockers were not given to most of the patients during the treatment. When the patient showed overt hyperthyroidism after the treatment, radioiodine treatment was repeated; however, some patients refused re-treatment. We evaluated thyroid function of the patients at 6 months, 1 year, and 2 years after the first treatment.

Radioiodine uptake

1.5 MBq of ^{131}I was administered 24 hours before RAIU measurement. RAIU of the thyroid was measured by a calibrated scintillation counter (Konan Electronics, Kobe, Japan). Spectroscopic measurement was performed for 1 minute with the patient positioned upright. The distance between the anterior surface of the neck and the detector was 35 cm. The count of remainder of the body was measured by shielding the neck. Resulting uptake was calculated using background radiation correction and reference standard: thyroid uptake = (neck counts – remainder of the body counts)/(reference counts – room counts)

Measurement of thyroid volume

The maximum width (W), the maximum thickness (T), and the maximum length (L) were measured in both lobes of the thyroid gland by ultrasonography. Thyroid volume was calculated by following formula: thyroid volume = $0.70 \times (Wr \times Tr \times Lr + Wl \times Tl \times Ll)$, in which the constant of 0.70 was obtained from the comparison of the thyroid volume measured by this method and the actual thyroid volume in 26 patients with Graves' disease [15].

Evaluation of thyroid function

TSH and FT4 concentrations in sera were measured by enzyme immunoassays (AxSYM TSH and AxSYM FT4, respectively; Abbott Japan Co., Tokyo, Japan). Normal ranges are 0.3–5.0 mU/L for TSH and 0.6–1.7 ng/dL for FT4. TBII was measured by radioreceptor assay using a TSH receptor antibody assay kit (RSR Ltd., Cardiff, UK).

Statistics

The baseline characteristics and results (FT4 levels and RAIU values) of the two groups of patients were compared using the χ^2-test for qualitative variables, or Mann-Whitney test for quantitative variables. Differences of outcomes were evaluated by the χ^2-test.

Results

RAIU in the 2-day ATD withdrawal group was 51.15 ± 11.08% (mean ± SD) and that in the 7-day group was 54.40 ± 9.64%. There was no significant difference between the 2 groups. The mean serum FT4 level measured on the first day of 24-h RAIU of the 7-day group was significantly higher than that in the 2-day group (2.10 ± 1.39 ng/dl vs. 1.27 ± 0.44 ng/dl; $p<0.001$) (Table 2). The maximum serum FT4 level was 2.73 ng/dl in the 2-day group and 6.00 ng/dl in the 7-day group.

Fig. 1 shows the outcomes in the 2 groups. The normal thyroid function includes subclinical hyperthyroidism and subclinical hypothyroidism. Patients with a normal thyroid function did not receive medication. There were no significant differences in the outcomes at each point between the 2 groups.

Table 1. Baseline Characteristics of patients with Graves' disease

	2-day withdrawal group	7-day withdrawal group
Sex (F/M)	29/14	39/10
Age (yr)	48.19 ± 13.41	48.37 ± 10.55
ATD (MMI/PTU)	35/8	46/3
Disease duration (yr)	7.19 ± 6.40	7.18 ± 7.21
Thyroid weight (g)	51.02 ± 23.09	45.73 ± 31.10
Total dose ^{131}I (mCi)	10.37 ± 5.91	8.90 ± 6.27
Dose frequency	1.35 ± 0.57	1.24 ± 0.43
Absorbed dose of ^{131}I (μCi/g)	101.14 ± 33.05	106.91 ± 31.81

Values are means ± SEM.
All values between the 2 groups showed no significant differences.
ATD: anti-thyroid drugs; MMI: methimazole; PTU: propylthiouracil.

Table 2. Comparison of RAIU and FT4 in the 2 groups

	2-day withdrawal group	7-day withdrawal group
24-h RAIU (%)	51.15 ± 11.08[a]	54.40 ± 9.64
FT4 at RAIU (ng/dl)	1.27 ± 0.44[b]	2.10 ± 1.39

Values are means ± SEM.
[a] P value for the comparison between groups was 0.1967.
[b] P value for the comparison between groups was <0.001.
Normal range for FT4 is 0.7–1.6 ng/dl.

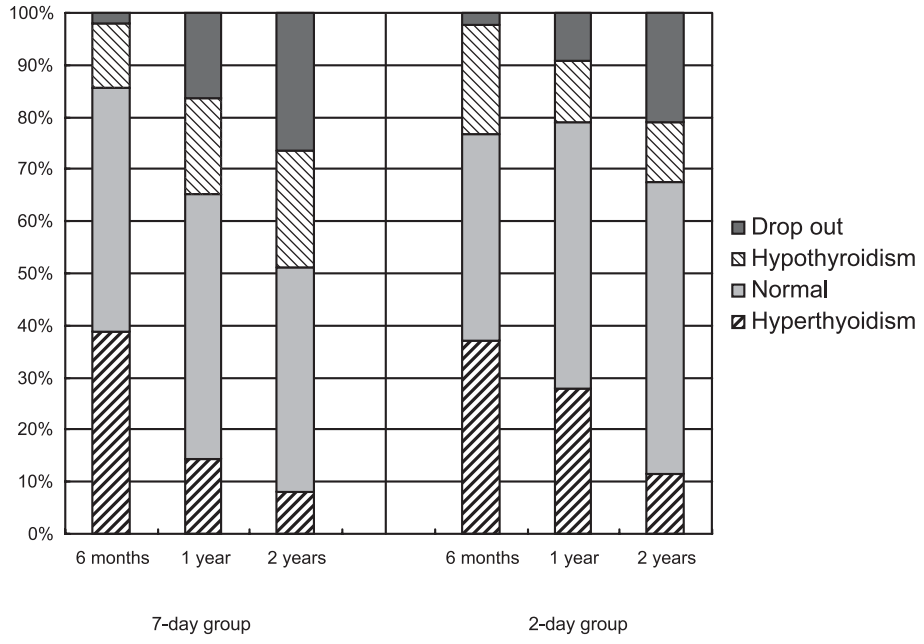

Fig. 1. Outcomes in the 2-day and 7-day ATD withdrawal groups. The normal thyroid function includes subclinical hyperthyroidism and subclinical hypothyroidism. There were no significant differences in the outcomes at each point between the 2 groups.

Discussion

Burch *et al.* reported that the short term elevation in thyroid hormone levels observed in patients with Graves' disease after radioiodine therapy is due to the discontinuation of ATD [2]. Moreover, Andrade *et al.* suggested that radioiodine therapy without ATD pretreatment could be safely carried out because serum thyroid hormone levels did not increase by radioiodine administration [1, 3]. The possibility that ATD medication reduces the efficacy of radioiodine therapy was also reported [8, 11, 12, 15]. The notion that the majority of patients with Graves' disease do not require ATD pretreatment before radioiodine therapy was supported by several reports [1–3, 16]. We also agree with this notion; however, we have to treat patients with ATD in cases of severe thyrotoxicosis and cardiac complications before radioiodine therapy. Additionally, radioiodine therapy is preferred as a second choice by most patients in some countries [6]. We have to consider the appropriate period of ATD discontinuation which does not alter the outcome of radioiodine therapy or exacerbate hyperthyroidism in these situations.

Various withdrawal periods before radioiodine therapy were reported [7–14]. Sabri *et al.* recommended discontinuing ATD at least 1 day before beginning radioiodine therapy [11, 12]. Walter *et al.* reported that withdrawal of carbimazole for 3 days provides a high enough RAIU and avoids the risk of exacerbation of hyperthyroidism [14]. A 2-day withdrawal period was supported by Moka *et al.* [17]. They reported that the negative kinetic effect of ATD can be compensated for by discontinuing medication 2 days before treatment. There have been no reports that compared the RAIU, serum thyroid hormone level at RAIU, and outcomes of radioiodine therapy between 2 different ATD withdrawal period groups, as presented in this study. Our results indicated that withdrawal of ATD for 2 days is superior to 7 days, because there were no significant differences in the outcomes between the 2 groups despite the exacerbation of hyperthyroidism in the 7-day group.

There were several patients with high serum FT4 levels that complained of severe hyperthyroid symptoms. The acute elevation of serum thyroid hormone seems to affect the patients. In order to prevent serum thyroid hormone increase after ATD withdrawal and radioiodine therapy, Bogazzi *et al.* suggested that lithium administration before therapy was useful [18]. A 2-day period of ATD withdrawal before radioiodine therapy along with lithium administration for high-risk patients may be more appropriate.

Our patients tend to think negatively of radioiodine therapy because they fear radioisotopes and permanent hypothyroidism without reason. It is for this reason that the administered dose of radioiodine in this study was smaller than the reported doses in other countries and cases of hyperthyroidism remained 2 years after radioiodine therapy. Since some patients were satisfied with the decreased goiter volume and dose of ATD, they did not desire additional radioiodine therapy. The reason why RAIUs in this study were lower than those reported in foreign countries is that dietary iodine is very rich in Japan. Dietary iodine restriction is a major issue in radioiodine therapy in Japan.

In summary, our results indicated that a 2-day ATD withdrawal period prior to radioiodine uptake sufficiently increased the uptake and did not exacerbate hyperthyroidism compared to 7-day withdrawal in Graves' disease patients. Furthermore, there were no significant differences in the outcomes between the 2 groups. We believe that the 2-day ATD withdrawal method may be useful for patients undergoing treatment with ATD who are to undergo radioiodine therapy.

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