Effect of long-term amiodarone treatment on thyroid function in euthyroid Japanese patients: a 12-month retrospective analysis

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Abstract. Amiodarone is an effective antiarrhythmic drug. However, it is associated with changes in thyroid function in euthyroid patients due to its high iodine content and intrinsic drug effects. Studies have been conducted in iodine-deficient and iodine-sufficient countries; however, data from countries with excessive iodine intake are lacking. Thus, this study aimed to evaluate the effect of long-term amiodarone treatment on thyroid function in euthyroid Japanese patients. Japanese adults aged ≥18 years who were treated with amiodarone for at least 90 consecutive days were included in this retrospective chart review. Patients with abnormal thyroid function test results at baseline were excluded. Serial changes in thyroid function tests at baseline and at days 30, 90, 180, 270, and 360 were analyzed using a mixed-effects model for repeated measures. In total, 46 patients with a mean age of 63.7 years were evaluated. The mean TSH level significantly increased from 1.62 μIU/mL at baseline to 3.43, 2.75, 2.84, 2.78, and 2.65 μIU/mL at days 30, 90, 180, 270, and 360, respectively. The mean free T₄ level significantly increased from 1.3 ng/dL at baseline to 1.4, 1.5, 1.5, 1.5, and 1.5 ng/dL at days 30, 90, 180, 270, and 360, respectively. The mean free T₃ level significantly decreased from 2.8 pg/mL at baseline to 2.4, 2.3, 2.3, 2.4, and 2.4 pg/mL at days 30, 90, 180, 270, and 360, respectively. In conclusion, significant changes in thyroid function persisted not only in the acute phase but also in the chronic phase of long-term amiodarone treatment.

Key words: Amiodarone, Thyroid, Japanese, Iodine

AMIODARONE is an effective antiarrhythmic drug used for the management of supraventricular and ventricular arrhythmias [1]. However, due to the high iodine content and intrinsic effects of this drug, it is associated with changes in thyroid function in euthyroid patients [2, 3]. Based on previous studies, in the acute phase, the serum TSH and free T₄ (FT₄) concentrations increased, whereas the serum free T₃ (FT₃) concentration decreased [2-4]. After 3 months of therapy, a steady state was achieved with the serum TSH concentration returning to baseline values. The serum FT₄ concentration remained slightly high or within the upper normal range, and the serum FT₃ concentration remained slightly low or within the lower normal range [2, 3, 5, 6].

Amiodarone-induced hypothyroidism (AIH) is more common in iodine-sufficient areas and amiodarone-induced thyrotoxicosis (AIT) in iodine-deficient areas. Thus, dietary iodine intake affects the risk of thyroid dysfunction [7, 8]. Japanese iodine intake from edible seaweeds is one of the highest worldwide, with an intake of approximately 1,000–3,000 μg/day [9]. Hence, it significantly exceeds the tolerable upper intake level of American adults (1,100 μg/day) [10]. Some reports have evaluated the prevalence and risk factors of AIH and AIT in Japanese patients [11, 12]. However, the changes in thyroid function over time remain unknown. Thus, the current study aimed to evaluate the effect of long-term amiodarone treatment on thyroid function in euthyroid Japanese patients.
Materials and Methods

Patients and methods

Japanese adults aged ≥18 years who were treated with amiodarone for at least 90 consecutive days at Keio University Hospital, Tokyo, Japan, between January 1, 2012, and February 26, 2019, were included in this retrospective chart review. The exclusion criteria were as follows: 1) patients with a history of thyroid disease and/or positivity for anti-thyroid antibodies; 2) those with palpable goiter; 3) those who did not undergo baseline thyroid function tests before the initiation of amiodarone; 4) those with abnormal baseline TSH or FT₄ values; 5) those who did not undergo thyroid function tests after the initiation of amiodarone; 6) those who developed AIH (elevated TSH level combined with a low or low-normal FT₃ level) or AIT (decreased TSH level combined with an elevated FT₃ level); and 7) those who initiated levothyroxine, methimazole, propylthiouracil, and/or prednisone at the attending physician’s discretion despite not meeting the definition for AIH or AIT. This study was approved by the ethical committee of Keio University School of Medicine (no. 20180297).

We collected data about the patients’ sex, date of birth, start and end of amiodarone therapy, thyroid function test results (TSH, FT₃, and FT₄ levels), anti-thyroid antibody results (antithyroid peroxidase [anti-TPO] antibody, antithyroglobulin [anti-Tg] antibody, thyroid-stimulating immunoglobulin, and TSH receptor antibody), and possible therapy for hypothyroidism and hyperthyroidism (levothyroxine, methimazole, propylthiouracil, and prednisone). Day 1 was defined as the day when amiodarone treatment was started, and the baseline value was the nearest date when the relevant data were available at or before day 1. Days 30, 90, 180, 270, and 360 were defined as the nearest date when the relevant data were available within days 7–45, 46–135, 136–225, 226–315, and 316–405, respectively.

Thyroid function test

TSH, FT₃, and FT₄ levels were measured using electrochemiluminescence immunoassay (ECLusys TSH, ECLusys FT₃, and ECLusys FT₄, respectively; Roche Diagnostics, Basel, Switzerland). The reference values were 0.30–4.50 μIU/mL for TSH level, 0.7–1.8 ng/dL for FT₃ level, and 2.0–4.5 pg/mL for FT₄ level.

Statistical analysis

The thyroid function test results were analyzed using a mixed-effects model for repeated measures with an unstructured covariance structure. Bonferroni correction was applied to adjust for multiple comparisons. TSH and FT₄ values were logarithmically transformed. A correlation analysis was performed using Spearman’s rank correlation coefficient. Two-sided p values <0.05 were considered statistically significant. All statistical analyses were performed using the Statistical Package for the Social Sciences software for Windows version 25.0 (IBM Corp., Armonk, NY, the USA).

Results

Participants

Of the 80 patients treated with amiodarone for at least 90 consecutive days, 4 had a history of thyroid disease, 14 did not undergo baseline thyroid function tests before the initiation of amiodarone, 9 had abnormal baseline TSH or FT₄ levels, 1 did not undergo thyroid function tests after the initiation of amiodarone, and 6 developed AIH (5 patients had a low FT₃ level and 1 patient had a low-normal FT₃ level (TSH 44.31 μIU/mL, FT₃ 0.9 ng/dL)). After excluding these patients, 46 (36 [78.3%] men and 10 [21.7%] women) patients with a mean (standard deviation [SD]) age of 63.7 ± 12.5 years were finally included in the analysis. Negative anti-thyroid antibody results were confirmed in 3 patients. The indication for amiodarone treatment was atrial tachyarrhythmia in 20 (43.5%) patients and ventricular tachyarrhythmia in 26 (56.5%) patients. The median (range) maintenance dose of amiodarone was 200 (100–400) mg/day at day 90.

Thyroid function test results

The mean TSH level increased from 1.62 μIU/mL at baseline to 3.43 μIU/mL on day 30, and it remained significantly high at 2.65–2.84 μIU/mL thereafter. The TSH level remained within the reference range during the observation period in 26 patients, was higher than the upper reference range at a single time point in 4 patients, and was higher than the upper reference range at more than two time points in 16 patients. The 95th percentile for the TSH level remained higher than the upper reference range during the observation period. The mean FT₄ level significantly increased from 1.3 ng/dL at baseline to 1.4–1.5 ng/dL thereafter, and the mean FT₃ level significantly decreased from 2.8 pg/mL at baseline to 2.3–2.4 pg/mL thereafter (Table 1 and Fig. 1). The results showed no significant correlation between TSH and FT₄ levels, with Spearman’s rank correlation coefficients of –0.128, –0.082, –0.167, –0.237, –0.223, and –0.100 at days 0, 30, 90, 180, 270, and 360, respectively (Fig. 2).

Discussion

In the current study, the FT₄ levels increased and the FT₃ levels decreased in euthyroid Japanese patients who received long-term amiodarone treatment. Although the
Mean TSH value remained within the reference range, there was a persistent increase in TSH level even in the chronic phase of amiodarone treatment.

Previous reports have attributed the changes in thyroid function to the high iodine content of amiodarone and its intrinsic drug effects, although the mechanisms are not fully understood [2, 3]. Amiodarone 200 mg contains 75 mg of organic iodine. Subsequent deiodination results in approximately 6 mg of free iodine released into circulation per day. Due to excessive iodine exposure, thyroid hormone synthesis is acutely inhibited (Wolff–Chaikoff effect) and causes an increase in serum TSH concentration.

Furthermore, the inhibitory effect of amiodarone on type 1 deiodinase activity, which blocks the conversion of T4 to T3 [2, 3].

Studies on serial thyroid function test results after long-term amiodarone treatment date back to the 1980s. In 1981, Melmed et al. [5] assessed 10 euthyroid men aged 56–70 years who were on long-term amiodarone treatment in California, the USA. The TSH levels (mean ± standard error [SE]) peaked after 8 weeks (5.3 ± 1.8 μU/mL) and returned to pretreatment baseline levels (1.6 ± 0.4 μU/mL) 3 months after the initiation of amiodarone. In 1986, Nademanee et al. [6] evaluated 76 patients (67 men and 9 women) with a mean age of 52 years in California, the USA. Of these patients, 68 remained euthyroid (solely based on the clinical criteria) while on long-term amiodarone treatment, and the TSH values (mean ± SD) did not change significantly at 1, 3, 6, 12, 18, and 24 months after the initiation of amiodarone (5 ± 4, 4 ± 3, 4 ± 4, 5 ± 4, 5 ± 3, and 3 ± 2 μU/mL, respectively) compared with baseline values (3 ± 2 μU/mL).

Neither study assessed the presence of anti-thyroid antibody. One study has evaluated the effect of amiodarone on thyroid function in Japanese patients. However, the study only assessed the thyroid function at a single time point, and the time period after the initiation of amiodarone was not identified [13].

In the current study, the persistent increase in TSH levels might be attributed to several factors. First, the study population included women, and the participants in this study were older than those in previous studies. Female sex and age are risk factors for elevated TSH levels [8, 14], and the larger proportion of female participants and those with older age might have affected the results. However, exploratory analyses excluding women and patients older than the mean age had similar results.

Second, the presence of anti-thyroid antibody was not assessed in most patients. In Japanese adults who underwent a general health checkup, 14.8% of men and 23.4% of women without palpable goiter tested positive for anti-TPO antibody or anti-Tg antibody. The prevalence of anti-TPO and anti-Tg antibodies was significantly higher in patients with hyperthyroidism and hypothyroidism than those in euthyroid patients [15]. Therefore, we excluded 34 (42.5%) patients with a history of thyroid disease and/or positivity for anti-thyroid antibodies, those with palpable goiter, those with abnormal or unmeasured baseline TSH or FT4 values, and those who developed AIH (defined as an elevated TSH level combined with not only a low FT4 level but also with a low-normal FT3 level). In addition, exploratory analyses excluding women, who generally have a higher rate of positive anti-thyroid antibodies, showed similar results.

### Table 1  Thyroid function test results at baseline and follow-up. The values were presented as mean, 95% confidence interval (those inside parenthesis), and 5th–95th percentile (those inside square brackets) from n observations.

|                      | Baseline | Day 30   | Day 90   | Day 180  | Day 270  | Day 360  |
|----------------------|----------|----------|----------|----------|----------|----------|
| TSH (μU/mL)          |          |          |          |          |          |          |
| n = 46               | 1.62*    | 2.75†    | 2.84†    | 2.78†    | 2.65†    |          |
| [0.68–3.84]          | (1.39–1.89) | (2.28–3.33) | (2.32–3.50) | (2.25–3.44) | (2.15–3.27) |          |
| FT4 (ng/dL)          |          |          |          |          |          |          |
| n = 46               | 1.3      | 1.5†     | 1.5†     | 1.5†     | 1.5†     |          |
| [1.0–1.7]            | (1.2–1.4) | (1.4–1.5) | (1.4–1.5) | (1.5–1.6) | (1.4–1.6) |          |
| FT3 (pg/mL)          |          |          |          |          |          |          |
| n = 46               | 2.8      | 2.3†     | 2.3†     | 2.3†     | 2.4†     |          |
| [1.8–3.6]            | (2.6–2.9) | (2.2–2.5) | (2.2–2.5) | (2.2–2.5) | (2.2–2.5) |          |
| n = 46               | 2.75     | 2.4†     | 2.4†     | 2.4†     | 2.4†     |          |
| [1.7–3.1]            | (1.6–2.9) | (1.5–3.2) | (1.5–3.0) | (1.4–3.2) | (1.3–3.5) |          |

* p < 0.05 and † p < 0.001 compared with values at baseline.
as described above. However, the presence of antithyroid autoantibodies might have affected the results, as it is a known risk factor for elevated TSH levels \[16\].

Third, Japanese are known for their excess iodine intake \[9\]. Although the mechanism of iodine-induced hypothyroidism remains unclear, failure to escape from the Wolff–Chaikoff effect is considered a factor \[17, 18\]. The results of studies evaluating the changes in thyroid function after iodine administration suggest that patients with greater iodine intake might have a slower recovery from the Wolff-Chaikoff effect. Namba et al. \[19\] administered 27 mg iodine for 4 weeks to 10 euthyroid Japanese men, observing significantly increased serum TSH concentration (mean ± SE) (2.43 ± 0.41 mU/L) compared to baseline values (0.95 ± 0.14 mU/L). Although not statistically significant, serum TSH concentration increased after 28 days of iodine withdrawal (1.35 ± 0.34 mU/L). Furthermore, Sang et al. \[20\] studied euthyroid Chinese participants with an initial median urinary iodine concentration of 291 μg/L (iodine intake “above requirements” according to World Health Organization [WHO] criteria \[21\]). In the 122 participants who received iodine supplementation ≥1,000 μg for 4 weeks, 49 developed subclinical hypothyroidism, which persisted in 14 of these subjects 1 month after iodine withdrawal. In contrast, Theodoropoulou et al. \[22\] studied 21 euthyroid participants in Greece, a country with “adequate” iodine intake \[23\], who received 80 mg iodine supplementation for 2 weeks. Serum TSH concentration (mean ± SD) increased significantly after 15 days of iodine administration (3.32 ± 1.60 mU/L) compared to baseline values (1.23 ± 0.40 mU/L). After 10 days of iodine withdrawal, the TSH concentration returned to the baseline value (1.24 ± 0.40 mU/L).

Fourth, inhibition of type 2 deiodinase activity in the chronic phase of amiodarone treatment might have played a role. Using mice with targeted disruption of the type 2 deiodinase gene, Rosene et al. \[24\] showed that the elevation in plasma TSH in amiodarone-treated mice depended on a functional type 2 deiodinase. Both amiodarone and its metabolite desethylamiodarone are non-competitive inhibitors of type 2 deiodinase, disrupting the transduction of the T4 signal, generating less T3, and weakening the TSH feedback mechanism. The underlying effect on TSH is likely to be at the pituitary gland given that paraventricular TRH mRNA levels decreased in amiodarone-treated mice \[24\].

The retrospective nature of the current study is its most important limitation, resulting in the lack of antithyroid antibody measurements. Furthermore, the study was performed at a single university hospital in Tokyo, and the sample size was small. Despite these limitations, this is the first study that evaluated the effect of long-term amiodarone treatment on serial thyroid function tests in euthyroid Japanese patients. Based on our personal experience during consultations, whether a high TSH level combined with high FT4 and low FT3 levels indicates a state of hypothyroidism or hyperthyroidism has caused confusion. In fact, amiodarone-treated patients with this biochemical profile are considered euthyroid, although hypothyroidism at the tissue level cannot be absolutely ruled out \[2, 3\]. While the idea of adding liothyronine (LT3) to maintain FT3 levels by bypassing the inhibitory effect of amiodarone on type 1

![Fig. 1](image.png) Serial changes in thyroid function tests. The black solid line indicates the mean ± 95% confidence interval. The red solid line indicates the 95th percentile. The blue solid line represents the 5th percentile. The broken lines indicate the upper and lower reference ranges for the thyroid function tests. * p < 0.05 and † p < 0.001 compared with values at baseline.
and type 2 deiodinase activity seems theoretically intriguing, the oral administration of LT3-containing tablets is followed by a spike of T3 in the circulation that peaks at around 2–3 hours [25]. This increase may provoke cardiac arrhythmias in susceptible patients [26]. Thus, as amiodarone-treated patients often have severe underlying cardiac disease, LT3 therapy is not recommended.

In conclusion, significant changes in thyroid function persisted not only in the acute phase but also in the chronic phase of long-term amiodarone treatment.

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Disclosure

None of the authors have any potential conflicts of interest associated with this research.
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