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Original Article

Risk factors for amiodarone-induced thyroid dysfunction in Japan ☆

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ABSTRACT

Background: Amiodarone is associated with a number of significant adverse effects, including elevated transaminase levels, pulmonary fibrosis, arrhythmia, and thyroid dysfunction. Although thyroid dysfunction is considered to be a common and potentially serious adverse effect of amiodarone therapy, the exact pathogenesis remains unknown because of its complex manifestations. Therefore, the prevalence of, and risk factors for, amiodarone-induced thyroid dysfunction in Japanese patients were investigated in the present study.

Methods: A retrospective analysis of patients treated with amiodarone between January 2012 and December 2013 was performed. A total of 317 patients with euthyroidism, or subclinical hyperthyroidism or hypothyroidism, were enrolled in this study.

Results: After being treated with amiodarone, 30 (9.5%) and 60 patients (18.9%) developed amiodarone-induced hyperthyroidism and amiodarone-induced hypothyroidism, respectively. Ten (33.3%) patients with amiodarone-induced hyperthyroidism and 40 (66.6%) with amiodarone-induced hypothyroidism were diagnosed within two years of the initiation of amiodarone therapy. Dilated cardiomyopathy (DCM) [Adjusted odds ratio (OR) 3.30 (95% confidence interval (CI): 1.26–8.90)], and cardiac sarcoidosis [Adjusted OR 6.47 (95% CI: 1.60–25.77)] were identified as predictors of amiodarone-induced hyperthyroidism. The baseline free thyroxine (T4) level [Adjusted OR 0.13 (95% CI: 0.03–0.68)], and thyroid-stimulating hormone (TSH) level [Adjusted OR1.47 (95% CI: 1.26–1.74)] were identified as predictors of amiodarone-induced hypothyroidism.

Conclusion: DCM and cardiac sarcoidosis were identified as risk factors for amiodarone-induced hyperthyroidism. Risk factors for amiodarone-induced hypothyroidism included higher baseline TSH level and lower baseline free T4 level, suggesting that subclinical hypothyroidism may be a potential risk factor for the development of amiodarone-induced hypothyroidism.

1. Introduction

Amiodarone is a potent antiarrhythmic drug that is widely used in the treatment and prophylaxis of various cardiac arrhythmias, including supraventricular and ventricular arrhythmias. However, amiodarone is associated with a number of significant adverse effects [1,2], including elevated transaminase levels, pulmonary fibrosis, arrhythmia, and thyroid dysfunction. Although thyroid dysfunction is considered to be a common and potentially serious adverse effect of amiodarone therapy [1,3], the exact pathogenesis remains unknown because of its complex manifestations [4]. The effects of amiodarone on the thyroid have been attributed to its iodine content and intrinsic properties [5]. Amiodarone is a benzofuran derivative containing 37.5% iodine by weight. Chronic treatment with amiodarone has been associated with a forty-fold increase in plasma and urinary iodide levels [6], which are responsible for thyroid dysfunction.

The exact incidences of amiodarone-induced hyperthyroidism and amiodarone-induced hypothyroidism currently remain unknown;

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however, the reported frequencies of amiodarone-induced hyperthyroidism and amiodarone-induced hypothyroidism vary widely from 0.8% to 37.8% [7–16] and from 1% to 32% [13,17–20], respectively. Although amiodarone-induced hypothyroidism is easily controlled by supplementation with L-thyroxine without requiring the discontinuation of amiodarone, the treatment of amiodarone-induced hyperthyroidism is more complex [21]. Amiodarone-induced hyperthyroidism is difficult to treat because of the large accumulation of iodine in the thyroid gland, and withdrawal of the drug is not effective because of its extremely prolonged half-life of 50–100 days [6,22]. Furthermore, the discontinuation of life-sustaining antiarrhythmic medication is not recommended for patients with life-threatening arrhythmias.

A younger age, male gender, thyroid autoantibody production, goiter, and low body mass index are associated with amiodarone-induced hyperthyroidism [12,13,16,23–25], while an older age, higher baseline thyroid-stimulating hormone (TSH) level, lower left ventricular ejection fraction, diabetes mellitus, and thyroid autoantibody production in women are possible risk factors for amiodarone-induced hypothyroidism [9,12,13,26–28]. Amiodarone-induced hyperthyroidism appears to occur more frequently in geographical areas with low dietary iodine intake, whereas amiodarone-induced hypothyroidism is more common in iodine-sufficient areas [26,29,30]. A daily iodine intake of 1–3 mg in Japan results in a six- to fifteen-fold excess over the recommended daily intake [31]. Therefore, a higher incidence of amiodarone-induced hypothyroidism may be more common than amiodarone-induced hyperthyroidism.

Meanwhile, subclinical thyroid dysfunction, defined as altered TSH and normal thyroxine (T4) levels, has been reported in more than 10% of patients with heart failure or dilated cardiomyopathy (DCM) [32–34]. This suggests that subclinical thyroid dysfunction is not so rare in patients with cardiovascular diseases treated with amiodarone, whereas previous reports regarding the prevalence of risk factors for amiodarone-induced thyroid dysfunction have focused only on patients with euthyroidism before amiodarone therapy [11,35]. Consequently, the impact of subclinical thyroid dysfunction on the development of amiodarone-induced hyperthyroidism and amiodarone-induced hypothyroidism is unclear.

The aim of the present study was to determine the prevalence of, and identify risk factors for, the development of amiodarone-induced hyperthyroidism and amiodarone-induced hypothyroidism in clinical practice, including not only patients with euthyroidism but also those with subclinical thyroid dysfunction. In addition, the impact of subclinical thyroid dysfunction on the development of amiodarone-induced hyperthyroidism and amiodarone-induced hypothyroidism was investigated.

2. Materials and methods

2.1. Study design and data collection

This retrospective cohort study was performed at the National Cerebral and Cardiovascular Center (NCVC) in Japan, which is a highly specialized medical center that treats cardiovascular diseases and related disorders, including cardiac diseases, hypertension, renal diseases, cerebrovascular diseases, and vascular disorders. The treatment of arrhythmias is an important task at the NCVC. Patients treated for arrhythmias with oral amiodarone between January 2012 and December 2013 were identified using the medical records and computer database of the hospital. The administration of amiodarone may cause transient thyroid dysfunction within three months of the initiation of therapy [36]. Therefore, only patients having thyroid function data at the baseline and more than three months after the initiation of amiodarone therapy were included in the study. Data from thyroid function tests performed within three months prior to the initiation of amiodarone therapy were used as baseline values. Patients without baseline data were excluded from the study. Patients diagnosed with thyroid dysfunction or treated with antithyroid drugs or thyroid hormone preparations at the initiation of amiodarone therapy, were excluded from the study. Demographic, clinical, and biochemical data, underlying cardiac diseases, the doses and durations of amiodarone and other medications, and the results of thyroid function tests were retrieved from the computerized hospital information system as well as medical records. The duration of amiodarone therapy was defined as the period between the initiation of amiodarone administration and the latest thyroid function tests. The duration of amiodarone therapy in patients who developed thyroid dysfunction during the study period was defined as the period between the initiation of amiodarone administration and when abnormal thyroid function was observed.

This study was approved by the Ethics Committees of the NCVC and Kinki University School of Pharmacy.

2.2. Definition of thyroid dysfunction

The incidence and pattern of thyroid dysfunction were exclusively based on laboratory diagnostic criteria. Serum TSH, free triiodothyronine (T3), and free T4 levels were measured using electrochemiluminescence immunoassay (Elecsys TSH, Elecsys FT3 III, Elecsys FT4 II; Roche Diagnostics, Japan). The normal reference ranges of thyroid function tests in our laboratory had previously been standardized as follows: free T4, 1.1–1.8 ng/dL; TSH, 0.5–5.5 μI U/mL. Patients were diagnosed with hyperthyroidism when a suppressed TSH level (<0.5 μI U/mL) was found in combination with an elevated free T4 level (>1.8 ng/dL). Patients with suppressed TSH (<0.5 μI U/mL) and normal free T4 (1.1–1.8 ng/dL) levels were considered to have subclinical hyperthyroidism. Hypothyroidism was diagnosed if the TSH level was elevated (>5.5 μI U/mL) and free T4 level reduced (<1.1 ng/dL), whereas patients with elevated TSH (>5.5 μI U/mL) and normal free T4 (1.1–1.8 ng/dL) levels were considered to have subclinical hypothyroidism. Patients with normal TSH levels were considered euthyroidism. Patients with a suppressed TSH level (<0.5 μI U/mL) in combination with a suppressed free T4 level (<1.1 ng/dL), and those with an elevated TSH level (>5.5 μI U/mL) in combination with an elevated free T4 level (>1.8 ng/dL), were designated “undetermined”.

Thyroid function tests performed more than three months after the initiation of amiodarone therapy were used to identify amiodarone-induced hyperthyroidism and amiodarone-induced hypothyroidism.

2.3. Statistical analysis

Descriptive statistics were expressed as the mean $\pm$ standard deviation (SD) for continuous variables, and as the number of cases and percentage (%) for categorical variables. Continuous variables were compared using ANOVA followed by Dunnett's post-test. Categorical variables were compared using the chi-squared test or Fisher's exact test. Univariate logistic regression analysis was used to assess the effect of each variable on amiodarone-induced hyperthyroidism and amiodarone-induced hypothyroidism. Multivariate logistic regression analysis was performed in order to assess the relationship between baseline clinical variables and the development of amiodarone-induced hyperthyroidism and amiodarone-induced hypothyroidism. All variables were entered into the logistic models and removed employing the stepwise backward elimination method if the P value exceeded 0.1. Adjusted odds ratios (ORs), their 95% confidence intervals (CIs), and P values were calculated. JMP®

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