Long-Term Efficacy of Amiodarone Therapy for the Prevention of Recurrence of Paroxysmal Atrial Fibrillation

Analysis Based on Patient Characteristics

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Summary

There is little information available on factors affecting the long-term prevention of paroxysmal atrial fibrillation (AF) in the Japanese population. A total of 71 patients (49 men, mean age, 68 ± 8 years) with paroxysmal AF refractory to ≥ 2 class I antiarrhythmic drugs received oral amiodarone (50-200 mg/day). All patients were observed for more than 12 months (mean follow-up period, 47 ± 26 months) and were analyzed on the basis of patient profiles. The percentage of patients with AF recurrence despite amiodarone therapy was 54% in all patients. In multivariate logistic regression analysis adjusted for age and sex, the following factors were associated with preventive efficacy for AF recurrence: left ventricular ejection fraction (LVEF) (relative risk [RR] 0.933, 95% confidence interval [CI] 0.877-0.993, \( P = 0.029 \)), asymptomatic AF (RR 0.068, CI 0.005-0.870, \( P = 0.039 \)), and AF occurring irrespective of circadian variation (RR 0.115, CI 0.013-0.988, \( P = 0.049 \)). The percentage of patients with conversion to permanent AF despite amiodarone therapy was 31% in all patients. In multivariate logistic regression analysis adjusted for age and sex, asymptomatic AF (RR 0.085, CI 0.010-0.732, \( P = 0.025 \)) was the only factor associated with preventive efficacy for conversion to permanent AF. Amiodarone appears to be effective in maintaining sinus rhythm, especially in patients with impaired left ventricular function. In contrast, amiodarone appears to be refractory in those with asymptomatic AF or AF occurring irrespective of circadian variation. (Int Heart J 2011; 52: 212-217)

Key words: Atrial fibrillation, Amiodarone, Prevention, Ejection fraction, Symptom

According to a large-scale epidemiological survey performed in western countries, atrial fibrillation (AF) is an independent risk factor for cardiovascular death, and the risk of such death is 2-3 times higher in patients with AF than in those with sinus rhythm. AF is often encountered in routine medical practice and is an arrhythmia that should be actively treated and controlled, because it not only causes cardiovascular complications, including thromboembolism and heart failure, but also decreases survival in patients with impaired left ventricular function. The number of patients with AF in the United States exceeded 5 million in 2000 and is expected to increase to threefold over the next 50 years. In Japan, the population is aging rapidly and the prevalence of AF among elderly persons aged 70 years or older is already around 3%. This is expected to increase to about 4.5% over the next 20 years.

We have previously reported a therapeutic limitation with class I antiarrhythmic drugs (AAD) in preventing recurrence of AF. In Japan, amiodarone (a class III antiarrhythmic drug) has been used to maintain sinus rhythm only in patients with paroxysmal and obstructive hypertrophic cardiomyopathy, although two large clinical trials have reported that the efficacy of amiodarone in preventing recurrence of paroxysmal and persistent AF is superior to that of class I antiarrhythmic drugs and dl-sotalol. The Japanese Circulation Society (JCS) Guidelines recommend that amiodarone be used as first-line therapy for preventing recurrence of paroxysmal AF associated with underlying heart disease and impaired cardiac function. However, there has been little information relating to clinical profiles that are suitable for amiodarone therapy from which to estimate the long-term efficacy of this drug in Japanese patients with paroxysmal AF. In the present study, we therefore examined the long-term efficacy of amiodarone therapy for the prevention of AF recurrence in patients with paroxysmal AF on the basis of patient clinical profiles.

Methods

Subjects: The subjects were 71 patients (49 men and 22 women, average age, 68 ± 9 years) who had symptoms such as palpitations and electrocardiographic evidence of AF corresponding to those symptoms. All patients visited the hospital every 2 to 4 weeks and were followed-up for more than one year.

Noninvasive examinations, including chest X-rays, exercise testing, and transthoracic echocardiography were per-
formed in all patients, while pulmonary function tests, computed tomographic examination of the brain and chest, and cardiac catheterization were performed at the discretion of the attending physician. Patients with severe bradyarrhythmia (sick sinus syndrome, atrioventricular block, or intraventricular conduction disorder), with hepatic or renal dysfunction associated with laboratory abnormalities, women with childbearing potential, and patients receiving concomitant T-type calcium antagonists were excluded from the study. This study was conducted between June 1997 and August 2009, and the mean observation period was 47 ± 26 months.

**Defibrillation protocol and antiarrhythmic drug therapy:** When AF had persisted for less than 48 hours, defibrillation was attempted immediately by drug therapy or electrical defibrillation under intravenous anesthesia with thiopental in accordance with the American Heart Association (AHA) guidelines.\(^\text{10}\) If AF had persisted for more than 48 hours in patients who were not on anticoagulant therapy, transesophageal echocardiography was performed to confirm that there was no left atrial thrombus or spontaneous echo contrast, after which defibrillation was performed and anticoagulant therapy with warfarin was added. If the patients were already receiving anticoagulant therapy, electrical defibrillation was performed after their PT-INR was confirmed to be between 1.6 and 3.0.

According to the protocol for preventing the recurrence of AF by AAD, patients with a left ventricular ejection fraction of more than 40% on echocardiography underwent medical or electrical defibrillation to restore sinus rhythm, and were subsequently randomized by the envelope method to either class Ia or Ib AAD (disopyramide 300 mg/day, aprindine 60 mg/day, or cibenzoline 300 mg/day) as first-line therapy. Patients were observed carefully for recurrence of AF, and if this was detected during follow-up, defibrillation was repeated at that time. Patients were subsequently randomized to receive either class Ic AAD (flecainide 150 mg/day or propafenone 150 mg/day) or bepridil (150 mg/day) as second-line therapy, and were observed carefully for recurrence. If AF recurred in patients on second-line therapy, amiodarone was administered if patient consent was obtained. In patients who withheld consent, a drug from Class I AAD that had not been used already was administered as third-line therapy. Patients whose left ventricular ejection fraction was less than 40% on transthoracic echocardiography underwent electrical defibrillation to restore sinus rhythm, and were subsequently treated with either aprindine (60 mg/day) or bepridil (150 mg/day) as first- or second-line therapy. If AF recurred despite such therapy, amiodarone was administered as a third-line drug at a starting dose of 400 mg/day for two weeks. After the initial loading phase, the maintenance dose of 50-200 mg/day was adjusted while the efficacy and side effects were monitored. The amiodarone dose was decreased at a rate of 50 mg/day step by step if recurrence of AF was not observed for 6 or 12 months. Patients were hospitalized for at least 2 weeks while undergoing initial amiodarone loading and follow-up was conducted 1 month after discharge, and then at intervals of 1-3 months. Baseline 12-lead ECG, echocardiography, thyroid and liver function tests, pulmonary function tests, ophthalmologic examination, and chest X-rays were performed for most patients before amiodarone therapy. Twelve-lead ECG was performed several times during the initial loading phase and also at each outpatient visit. Thyroid and liver function testing, pulmonary function testing, and chest X-rays were used to access the adverse effects of amiodarone therapy at week 2, months 1 and 3, and then every 6 months after initiation. Ophthalmologic examination was performed every 6 months.

Two to four weeks after commencement of or alteration in an oral antiarrhythmic drug, standard 12-lead ECG and ambulatory 24-hour monitoring were recorded in all patients. In addition, at every visit to our outpatient clinic, maintenance or otherwise of sinus rhythm was confirmed with the use of a portable ECG monitor (IEC-1101 “Heart Mate”, Nihon Kohden Corporation). Whenever palpitations occurred, an ambulatory 24-hour monitoring was recorded at the discretion of the attending physician to determine whether AF had recurred or not.

**Definitions:** Based on symptoms and ambulatory 24-hour monitoring, paroxysmal AF was defined as transient AF terminating spontaneously within 1 week of onset.\(^\text{11}\) The history of AF was the period from the initial episode of AF to the time of the initiation of antiarrhythmic therapy. Permanent AF was defined as AF that was refractory to pharmacological and electrical cardioversion and did not convert to sinus rhythm for a period greater than 6 months. Asymptomatic AF was defined as an AF episode in which patients had none of the symptoms associated with arrhythmia such as palpitations, dizziness, chest discomfort or syncope, or heart failure symptoms such as dyspnea, edema, orthopnea, or paroxysmal nocturnal dyspnea at initial hospital visit.\(^\text{12}\) Cerebral thromboembolism was diagnosed in all cases based on typical neurological symptoms and the development of a new low-density lesion greater than 3 mm on brain computed tomographic examination or magnetic resonance imaging, which was performed in all patients. Hypertension was defined according to the Japanese Society of Hypertension Guidelines for the Management of Hypertension (JSH 2009).\(^\text{13}\) Diabetes mellitus was diagnosed if fasting venous blood glucose was ≥ 126 mg/dL or hemoglobin A1C was ≥ 6.5%. Onset of paroxysmal AF was classified as the diurnal (07:00 to 17:00), nocturnal (17:00 to 07:00 next morning), or mixed type (AF occurring irrespective of circadian variation) based on standard 12-lead ECG and ambulatory 24-hour monitoring findings. In patients with AF at the time of hospital visits, classification was based on the time when symptoms commenced.\(^\text{14}\) Recurrence of AF was not determined from subjective symptoms, but was defined as the time when ECG first revealed AF during antiarrhythmic drug therapy. In the pulmonary function test, we regarded FEV1.0 ≤ 70% as a diagnostic criterion for chronic obstructive pulmonary disease. Risk factors for thromboembolism regarding CHADS2, scores were defined as a history of cerebral infarction or transient ischemic attack, hypertension, diabetes mellitus, coronary artery disease, or recent heart failure.\(^\text{10}\)

**Statistical analysis:** Continuous data are expressed as the mean ± standard deviation (SD). Between-group comparisons were performed using the Mann-Whitney U-test for continuous variables and the chi-square test for noncontinuous variables. The independent predictors for recurrence and conversion to the permanent form of paroxysmal AF were analyzed by multivariate logistic regression analysis. In all of these tests, \(P\) values < 0.05 were identified as significant differences.
RESULTS

Comparison of subject baseline profiles estimated by preventive efficacy of AF recurrence: The percentage of patients with and without AF recurrence during amiodarone therapy was 54% (n = 38 patients, group I) and 46% (n = 33 patients, group II), respectively, in all 71 patients during the follow-up period. The incidence of asymptomatic AF was significantly higher in group I (24%) than in group II (3%) (P < 0.05, Table I). The incidence of concomitant RAAS inhibitors was significantly lower in group I (24%) than in group II (64%) (P < 0.05, Table II). In contrast, left ventricular ejection fraction (LVEF) was significantly higher in group I (65.9 ± 13.0%) than in group II (57.6 ± 14.0%) (P < 0.05, Table II). Other demographic data showed no significant differences.

Predictors of preventive efficacy for AF recurrence during amiodarone therapy: Multivariate logistic regression analysis adjusted for age and sex revealed that LVEF (relative risk 0.933, 95% confidence interval 0.877-0.993, P = 0.029), asymptomatic AF (0.068, 0.005-0.870, P = 0.039), and AF occurring irrespective of circadian variation (0.115, 0.013-0.988, P = 0.049) were associated with preventive efficacy for AF recurrence (Table III).

Comparison of subject baseline profiles estimated by preventive efficacy of conversion to permanent AF: The percentage of patients with and without conversion to permanent AF during amiodarone therapy was 31% (n = 22 patients, Group III) and 69% (49 = patients, Group IV), respectively, in all 71 patients during the follow-up period. The incidences of diabetes mellitus and asymptomatic AF were significantly higher in Group III (32% and 36%, respectively) than in Group IV (6% and 4%, respectively) (both P < 0.05, Table IV). The incidence of concomitant RAAS inhibitor use was significantly lower in Group III (18%) than in Group IV (57%) (P < 0.05, Table V). In contrast, left ventricular ejection fraction (LVEF) was significantly higher in Group III (67.8 ± 12.4%) than in Group IV (59.4 ± 14.1%) (P < 0.05, Table IV). Other demographic data showed no significant differences.

Predictors of preventive efficacy for conversion to permanent AF during amiodarone therapy: Multivariate logistic regression analysis adjusted for age and sex showed that asymptomatic AF (0.085, 0.010-0.732, P = 0.025) was associated with preventive efficacy for conversion to permanent AF only (Table VI).

Adverse effects: The incidence of intolerable noncardiac effects resulting in withdrawal of the drug during oral amiodar-
One therapy was 5.6% in all cases during the mean follow-up period of 47 ± 26 months. We did not experience any fatal adverse events, although amiodarone therapy was discontinued due to pulmonary toxicity in 3 cases and skin eruption in 1 case.

**DISCUSSION**

**Pharmacological effects of amiodarone:** The pharmacological effects of amiodarone on single myocardial cells include inhibition of the Ito, Iks, Ik1, and Ikach channels as well as the IKur channel specific to atrial muscle cells, which results in prolongation of the atrial refractory period. While the current density of the Ito and Iks channels varies depending on the site within the myocardial tissue, which contributes to the non-uniformity of action potential duration over the myocardium, amiodarone blocks these channels to decrease the non-uniformity of the atrial refractory period and also has beta-blocking and If-channel blocking activities. These properties make this drug a multichannel blocker. Some reports have indicated that amiodarone not only has potent antiarrhythmic effects but also exerts beneficial effects on cardiac hemodynamics. Because of its alpha- and beta-sympathetic blocking actions, its inhibition of the production of cytokines such as tumor necrosis factor (TNF)-alpha, interleukin (IL)-6, IL-8, and monocyte chemoattractant protein (MCP)-1, its antioxidant property to inhibit the generation of active oxygen, and its inotropic action via increased intracellular Ca concentrations due to its Na-K pump inhibitory effect, amiodarone is expected to provide therapeutic effects in patients with AF where onset is closely related to cardiac hemodynamic deterioration.

**Clinical effects of amiodarone:** In patients with impaired cardiac function, it has been reported that the prevalence of AF increases as the severity of heart failure increases. Class I antiarrhythmic drugs, which are widely used in Japan, have a negative inotropic effect and it has therefore been reported that long-term treatment with such drugs is associated with worsened prognosis in patients with AF who have impaired left ventricular function. In contrast, amiodarone is believed to have a minimal negative inotropic effect and fewer proarrhythmic effects than other class I antiarrhythmic drugs. Moreover, it has been reported that two years of amiodarone therapy improved left ventricular ejection fraction in patients with congestive heart failure participating in a large-scale controlled clinical trial. A recent study has shown that amiodarone therapy significantly improved left ventricular ejection fraction in patients with congestive heart failure participating in a large-scale controlled clinical trial.
study and that long-term amiodarone therapy for more than two years prevented the progression of left atrial enlargement in patients with paroxysmal AF. In this study, left ventricular ejection fraction was found to be an independent predictor of recurrent AF after oral amiodarone therapy, and it was shown that amiodarone therapy would be more effective in preventing recurrences of AF in patients with reduced cardiac function than in those with normal cardiac function. On the other hand, it was difficult to maintain sinus rhythm even after amiodarone therapy in patients with mixed type AF occurring irrespective of circadian variation or those with asymptomatic AF, and this result was consistent with our previously reported long-term study results on class I antiarrhythmic drugs in such patients with paroxysmal AF. Ueng, et al demonstrated that an independent predictor for the maintenance of sinus rhythm in patients with long-standing persistent AF was left atrial dimension > 40 mm prior to electrical cardioversion at a mean follow-up period of 270 days. Our study, in contrast, showed that LVDd and LAD in patients with paroxysmal AF refractory to ≥ 2 class I antiarrhythmic drugs were not associated with independent predictors for the preventive efficacy of AF recurrence or conversion to permanent AF at a mean follow-up period of 47 ± 26 months. This inconsistency may have resulted from differences in the subjects, follow-up periods, mean doses of amiodarone, and incidence of concomitant RAAS inhibitors between the two studies.

Tachycardic episodes are easily overlooked in patients with asymptomatic AF who do not visit medical institutions as the symptoms are both rare and subjective; it is thus likely that AF has already been present for a long period of time. Since the duration of AF leads to a vicious circle of “atrial electrophysologic remodeling,” AF tends to recur more frequently and eventually becomes a chronic (permanent) condition. In a previous study, we reported that failure to convert to sinus rhythm early after recurrence of AF impaired the subsequent therapeutic response to antiarrhythmic drugs. This finding is believed to explain why it is more difficult to prevent asymptomatic AF than symptomatic AF. In addition, mixed type AF occurring irrespective of circadian variation is considered to be less related to autonomic nerves, but more related to the influence of degeneration or fibrosis of atrial muscles themselves. It is therefore easy to predict that AF will become increasingly refractory to antiarrhythmic drug therapy as the myocardial lesion progresses.

In the 1980s, the administration of high doses of amiodarone was identified as a major cause of pulmonary toxicity. The initial large study in 1990 demonstrated the incidence rate reached 9.1% at 60 months of amiodarone therapy in patients receiving a daily dose of 400-500 mg. It is commonly considered that low-dose amiodarone therapy is safer. The incidence of amiodarone-induced pulmonary toxicity was recently reported to be 2.1% per year in 500 Japanese patients on low maintenance doses of less than 200 mg daily, which is not low compared with the 1.8% per year in a meta-analysis of 6,500 American and European patients in placebo-controlled amiodarone trials. Other studies in small numbers of Japanese patients with atrial tachycardia found that 2.7-3.6% of patients receiving amiodarone developed pulmonary toxicity during mean follow-up periods of 30-36 months. In the present study, the incidence of pulmonary toxicity was 1.4% per year, which is not low in comparison to American and European data. These findings suggested that we should reduce the incidence of amiodarone-induced pulmonary toxicity because there is no safe dose of amiodarone therapy, at least in Japanese patients. It is, therefore, important to check suitable screening tests for their efficacy and adverse effects as soon as possible to detect pulmonary toxicity during long-term amiodarone therapy.

Limitations: The present study has the following limitations: First, as this was a retrospective observation study, some bias may exist in the demographic data of each respective group. It is believed to be difficult to administer amiodarone to patients randomly as the first-choice drug for paroxysmal AF in routine practice in Japan because pulmonary toxic effects such as interstitial pneumonia occur at an incidence of about 2.1% yearly. Secondly, recurrence of AF was diagnosed at the time of detection of AF on ECG. A study using ambulatory 24-hour monitoring reported that more than half of tachycardic episodes were not recognized by patients with paroxysmal AF who had obvious symptoms. On the other hand, a study using an ambulatory ECG monitor (Cardiophone) reported that 30 to 70% of patients with symptomatic AF developed sinus tachycardia or premature atrial contraction when they complained of palpitations. In other words, present detection methods based on ECG findings have methodological limitations in accurately detecting AF recurrence. Thirdly, since amiodarone is a multichannel blocker, it is not known which pharmacological action of the drug was effective in each case. Fourth, since the present study targeted patients with paroxysmal AF only, it was not known how amiodarone was effective in preventing sustained AF. Lastly, the sample size of the present study was relatively small.

It will therefore be necessary to conduct a prospective controlled multicenter study in Japan in order to reevaluate the efficacy and safety of amiodarone in a larger patient population with paroxysmal and persistent AF. Conclusion: Amiodarone appears to be an effective therapy for patients with impaired left ventricular function and paroxysmal AF. However, it is less effective in those with asymptomatic AF or AF occurring irrespective of circadian variation.

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