Efficacy of Amiodarone for Preventing the Recurrence of Symptomatic Paroxysmal and Persistent Atrial Fibrillation After Cardioversion

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Background  It has been previously reported that the efficacy of class I antiarrhythmics in preventing the recurrence of symptomatic paroxysmal and persistent atrial fibrillation (AF) is limited when AF lasts for 48 h or more. However, it is unclear whether the efficacy of amiodarone, a class III drug, is superior to class I antiarrhythmics in patients with long-lasting AF.

Method and Results  The relationship between the duration of tachycardia and the efficacy of amiodarone in preventing recurrence of tachycardia was examined in 55 patients (37 men, 18 women, mean age 68±9 years) to whom amiodarone was administered after electrical or pharmacological cardioversion for paroxysmal and persistent AF. In 26 patients, paroxysmal and persistent AF ceased within 48 h after onset (Group A), and in the other 29 patients, it ceased after 48 h (Group B). Patient characteristics and actuarial recurrence-free rates were compared between the 2 groups. The mean follow-up period was 30±11 months. No statistically significant difference between the groups was found in patient characteristics. Actuarial recurrence-free rates in Group A and B at 1, 3, 6, 9, and 12 months were 100%, 81%, 69%, 62%, and 54%, and 93%, 79%, 66%, 52%, and 48%, respectively (p=NS at 12 months). The period of maintenance of sinus rhythm was 14.7±3.2 months in group A and 13.3±3.3 months in group B (mean ± SE, p=NS).

Conclusion  In the case of amiodarone, efficacy for maintaining sinus rhythm after cardioversion of AF was not biased by the duration of arrhythmia. This observation suggests amiodarone is effective in maintaining normal sinus rhythm after cardioversion, even in patients with long-lasting AF and electrical atrial remodeling.

Key Words: Amiodarone; Atrial fibrillation; Prevention; Remodeling

With the rapidly increasing average age of Japanese society, there is no doubt that the prevalence of atrial fibrillation (AF) will rise in the future. According to epidemiologic research in the United States, the number of patients suffering from AF is estimated to increase 2.5-fold in the next 50 years.1 AF not only decreases quality of life,2 but also complicates thromboembolism or heart failure (HF).3,4 In addition, AF worsens the prognosis of patients with impaired cardiac function and of the elderly.5,6 Recently it was indicated that if sinus rhythm (SR) can be maintained for a long time without recurrence of AF, the rate of adverse cardiovascular events thereafter decreases and prognosis improves.7,8 However, the class I antiarrhythmic drugs have a therapeutic limitation.9 We previously reported that the efficacy of cibenzoline and disopyramide in preventing recurrence of paroxysmal AF in patients in whom AF lasted for 48 h or more was inferior to that in those in whom AF lasted for less than 48 h before cardioversion.10,11 Amiodarone, regarded as a class III anti-arrhythmic drug, has been used to maintain SR only in Japanese patients with paroxysmal and obstructive hypertrophic cardiomyopathy, even though 2 large clinical trials have reported that the efficacy of amiodarone in preventing recurrence of paroxysmal and persistent AF is superior to that of the class I antiarrhythmic drugs and dl-sotalol.12,13 Amiodarone is considered to have a multi-channel blocking action affecting potassium, calcium and sodium channels, in addition to β-adrenergic receptors. The upregulation of various ion channels occurs gradually in atrial muscle after prolonged rapid atrial pacing in experimental models14 and amiodarone is considered to have a pharmacological action that blocks those upregulated ion channels. The importance of this mechanism of action is unclear, however, in relation to the efficacy of amiodarone in preventing recurrence of paroxysmal and persistent AF that is defibrillated late after the initiation of the arrhythmia.

In the present study we examined the effect of the duration of AF before cardioversion on the subsequent efficacy of amiodarone in preventing recurrence of tachycardia in patients with paroxysmal and persistent AF.

Methods

Subjects
The study included 55 patients (37 men, 18 women, mean age 68±9 years) who have subjective symptoms of palpitation and who had electrocardiographically confirmed AF.

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All patients were followed once or twice a month at the outpatient clinic of Iwate Medical University School of Medicine and at every visit it was ascertained by the symptoms and electrocardiography (ECG) findings whether SR was maintained without recurrence of AF or if AF had recurred. Ambulatory 24-h ECG recording was repeated at a 3-month interval or when it was considered to be necessary by the physician. In this study, the range of duration of AF was from more than 2 h to 56 days (mean duration 118.2±304.6 h) and the mean frequency of attacks was 3.1±1.2 times. All patients submitted a clinical history and underwent chest radiography, exercise radionuclide angio- graphy, and echocardiography. Pulmonary function testing, chest computed tomography (CT), and intracardiac catheter testing were performed in some patients at the request of attending physicians. Paroxysmal AF was defined as AF terminating spontaneously within 7 days of onset. Persistent AF was defined as AF lasting from 7 days to 6 months, and also requiring pharmacological or electrical cardioversion for restoration of SR. In the present study, the paroxysmal AF group consisted of 40 patients (73%) and persistent AF affected 15 patients (27%). For all the patients cerebral thromboembolism was diagnosed by clinical manifestations and the confirmation of an infarct lesion larger than 3 mm on CT or magnetic resonance imaging.

Chronic AF was defined when the condition was refractory to treatment (SR was never observed continuously for 6 months, despite administration of multiple antiarrhythmic drugs). Hypertension was defined by blood pressure, measured at any time, with systolic pressure greater than 160 mmHg and diastolic pressure greater than 95 mmHg.

The time of onset of paroxysmal and persistent AF was defined according to the time of equivalent symptom onset in patients in whom AF was observed in recorded findings by a cardiac monitor, ambulatory 24-h monitor, or during the consultation. The classifications were diurnal type (07.00 h to 17.00 h), nocturnal type (17.00 h to 07.00 h next morning), and mixed type (symptoms appeared at any time).

Patients who had severe bradycardia (sick sinus syndrome, atrioventricular block, and intraventricular conduction disturbance), hepatic or renal dysfunction observed as abnormal test results, those receiving β-blockers, those who had asymptomatic AF, and women who may have become pregnant were excluded from the study population.

The study was conducted during June 1993 through August 2002. The total mean follow-up period was 48.4±29.0 months.

Protocol for Cardioversion

The protocol to prevent recurrence of paroxysmal and persistent AF using antiarrhythmic therapy was followed according to the American Heart Association (AHA) guideline. For patients with duration of AF of less than 48 h, we immediately attempted pharmacological or electrical cardioversion under thiopental intravenous anesthesia. Before publication of the AHA guideline for AF management patients with duration of AF of 48 h or more underwent early pharmacological or electrical cardioversion after confirmation that neither intracardiac thrombus nor “moyamoya” echo existed on transesophageal echocardiography. After the AHA guideline was issued, cardioversion was performed together with anticoagulant therapy using warfarin pre- and post-cardioversion for 3 weeks and 4 weeks, respectively.

Protocol for Antiarrhythmic Therapy

The patients who had a left ventricular ejection fraction (LVEF) of at least 40% confirmed by echocardiography underwent medical defibrillation or cardioversion. After conversion to SR, these patients were given a class Ia or Ib drug as the first-choice drug (disopyramide 300 mg/day, aprindine 60 mg/day, or cibenzoline 300 mg/day) by randomized allocation and were carefully observed for manifestation of recurrence. If AF recurred during follow-up, cardioversion was performed again, followed by randomized allocation of a class Ic agent (flecainide 150 mg/day or pilscainide 150 mg/day) or bepridil 150 mg/day as the second-choice drug, and the patients were again carefully observed for recurrence of AF. If there was recurrence during the follow-up period after administration of the second-choice drug, amiodarone was administered to consenting patients.

The patients whose LVEF was less than 40% confirmed by echocardiography underwent cardioversion. After conversion to SR, these patients were given either aprindine 60 mg/day or bepridil 150 mg/day by randomized allocation as the first- and second-choice drugs. If recurrence of AF was observed with either drug, amiodarone was administered to consenting patients. These patients were loaded with oral amiodarone at a dose of 400 mg/day for 14 days. After the initial loading phase, the maintenance dose of 50–200 mg/day was adjusted while the efficacy and side-effects were monitored, decreasing amiodarone at a dose of 50 mg/day stepwise if recurrence of AF did not occur for 12 months. Patients were hospitalized for at least 2 weeks while undergoing the initial amiodarone loading and follow-up was continued for 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-ray 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-ray was used to monitor the adverse effects of amiodarone therapy at week 2, month 1 and 3, and then every 6 months after initiation. Ophthalmologic examination was performed every 6 months. All patients underwent standard 12-lead ECG and ambulatory 24-h monitoring after 2–4 weeks of selected antiarrhythmic drug initiation or alteration of drug choice. The maintenance of SR was confirmed at every visit by portable ECG monitor (IEC-1101 ‘Heart Mate’, manufactured by Nihon Koden Corp, Japan). Recurrence was determined as the time point when AF was first confirmed with ECG after the patient began taking oral amiodarone.

Patients were divided into 2 groups based on the duration of AF before cardioversion: less than 48 h as Group A, and 48 h or more as Group B. The groups were compared for clinical characteristics, duration for maintenance of SR and actuarial recurrence-free rates. We also retrospectively analyzed the efficacy of amiodarone therapy in preventing recurrence of AF of the patients in whom AF lasted for 1 week or more. Patients in Group B were divided into 2 groups based on the duration of AF before cardioversion: less than 1 week as Group B-I, and 1 week or more as Group B-II.

Statistical Analysis

The results for clinical characteristics are mean value±
Results

Patient Clinical Characteristics (Table 1)

Among the 55 cases of paroxysmal and persistent AF, the mean duration of AF for Groups A and B was 18.6±14.3 h and 502.1±534.9 h, respectively. No significant difference was observed between the 2 groups in age, sex, smoking habit, hypertension, diabetes, hyperlipidemia, hyperuricemia, alcohol history, duration from incipient symptom, underlying cardiopulmonary disease, cerebral thromboembolism, permanent AF, history of HF, administration of angiotensin converting enzyme inhibitors, left ventricular end-diastolic dimension, left atrium dimension,
LVEF, number of antiarrhythmic drugs, or the time of onset. Underlying cardiac diseases observed in Group A were ischemic heart disease (n=4), dilated cardiomyopathy (n=3), cardiac valvular disease (n=3) and hypertrophic cardiomyopathy (n=2). Group B had ischemic heart disease (n=7), dilated cardiomyopathy (n=6), cardiac valvular disease (n=2) hypertrophic cardiomyopathy (n=1), and atrial septal defect (n=1).

**Actuarial Recurrence-Free Rates in Groups A and B (Fig 1)**

No significant difference was found between the 2 groups in actuarial recurrence-free rates. The rates at 1, 3, 6, 9 and 12 months were 92.9%, 85.7%, 71.4%, 64.3%, and 57.1%, respectively, in Group A, and 93.1%, 79.3%, 65.5%, 51.7% and 48.3%, respectively, in Group B.

**Maintenance of SR in Groups A and B (Fig 2)**

No significant difference was found between 2 groups in the mean period of maintenance of SR: 14.7±3.2 months in Group A and 13.3±3.3 months in Group B.

**Actuarial Recurrence-Free Rates in Groups B-I and B-II (Fig 3)**

No significant difference was found between these 2 groups in actuarial recurrence-free rates. The rates at 1, 3, 6, 9 and 12 months were 92.9%, 71.4%, 57.1%, and 46.7%, respectively, in Group B-I, and 86.7%, 73.3%, 53.3%, 47.7%, and 40.0%, respectively, in Group B-II.

**Adverse Effects**

The incidence of intolerable non-cardiac effects resulting in withdrawal of oral amiodarone therapy was 5.5% in all cases during the follow-up periods. We did not have any fatal adverse events, but amiodarone therapy was discontinued because of pulmonary fibrosis in 2 cases, and skin eruption in 1 case.

**Discussion**

In the present study we examined and compared the efficacy of oral administration of amiodarone on the recurrence-free rates of paroxysmal and persistent AF for 2 groups of tachycardia: less than 48 h and 48 h or more. According to the AHA guideline, the method of treatment of AF changes after 48-h duration of the arrhythmia. If AF has been present for less than 48 h, immediate defibrillation is preferred; if the duration is 48 h or more, it is recommended to perform cardioversion after administration of adequate anticoagulant therapy. Therefore, clinically, the efficacy of antiarrhythmic therapy to prevent recurrence of AF after defibrillation is evaluated with 48 h as the boundary. The present study has demonstrated that the recurrence-free rate of the patients treated with amiodarone therapy at 12 months in Group A was similar to that in Group B, which suggests that the efficacy of oral amiodarone therapy in preventing recurrence of AF was not affected by the duration of arrhythmia. In contrast, we reported that class I antiarrhythmic drugs, such as disopyramide and cibenzoline, showed less efficacy in preventing recurrence of AF in patients whose duration of tachycardia was 48 h or more compared with similar patients in whom the duration was less than 48 h. Thus, amiodarone may have favorable pharmacological actions for preventing the recurrence of AF for which class I antiarrhythmic drugs are ineffective.

The mechanism of the efficacy of amiodarone could not be proven from the results of the present study; however, the following hypothesis does explain it. Amiodarone prolongs the refractory period by inhibiting the transient outward potassium current (Ito), late rectifying potassium current (Is), inwardly rectifying potassium current (Iks), acetylcholine activated potassium current (Ikach) and ultrarrapid delayed rectifier current (Ikr) ion channels, which are characteristic of atrial muscle cells. The Ito and Iks channels have different current densities, depending on their site in cardiac muscle tissue, and this contributes to the non-uniformity of the duration of the action potential. Amiodarone is a multi-channel blocking agent that also decreases the non-uniformity in the atrial refractory period effects a β-blocking action and also blocks the action of the hyperpolarization-activated inward current (Ih) channel. Furthermore, because amiodarone blocks the channels that are upregulated by remodeling, such as Ii, Ih, and Iks, or by hyperreactivity of the sympathetic nervous system, it is thought that its pharmacological action is well suited to treat patients with long-standing persistent tachycardia. Furthermore, mibefradil, a T-type Ca antagonist, is said to be a channel blocker that possibly prevents remodeling experimentally produced by frequent pacing. Amiodarone
is also reported to be an antiarrhythmic drug that possibly prevents experimental remodeling, and reportedly it is its coexisting T-type Ca antagonistic action that exerts the favorable influence.

Study Limitations
First, there was no placebo group; however, all patients were symptomatic and required antiarrhythmic drugs therapy. According to reports from the United States and Europe in which the rates for maintenance of SR in patients with paroxysmal and persistent AF were examined in a placebo group, significant differences were observed depending on the follow-up period; 7% at 1 month; 30% at 2 months; and 20% at 3 months. There is also a possibility that differences in the patients’ characteristics might influence the efficacy of antiarrhythmic drug therapy. In our study, the subjects were limited to those who were available for more than 12-month follow-up, a relatively long time, and were refractory to 2 or more class I antiarrhythmic drugs. Therefore, we consider that the influence of recurrence-free rates, as found in a placebo group, on the results of our study would be quite small.

Second, we only included patients with symptomatic AF; however, not all of these patients were clearly aware of their tachycardia attack. Analysis of ambulatory 24-h ECG showed that even patients with symptomatic AF were unaware of more than half of their tachycardia events and therefore the precise time of the initial recurrence of AF might have been missed. In addition, 30–70% of the patients who complain of palpitations among patients with symptomatic AF have sinus tachycardia or atrial extrasystole, according to an analysis with portable ECG monitor (Cardiophone). It is impossible to determine the time of recurrence of AF precisely when depending only on the subjective symptoms reported by patients. Therefore, there is a methodological limitation to determining the time of recurrence of AF, even if we use both subjective symptoms and ECG findings. Third, the total number of patients was relatively small. More patients are required to draw a definite conclusion in terms of the efficacy of oral amiodarone therapy in Japanese patients with AF. Fourth, this study recruited only patients with AF refractory to 2 class I drugs or more who had impaired quality of life due to AF-induced severe symptoms and/or congestive HF after recurrence of AF. This could be a major selection bias compared with routine outpatient therapy in patients with AF. Finally, we set the boundary for the duration of AF at 48 h and 1 week to estimate the relationship between the efficacy of amiodarone therapy and the duration of tachycardia. However, electrical and structural remodeling progresses gradually during tachycardia, and irreversible structural changes in atrial muscle could be eventually observed in the long term. Different results might be drawn if we set a longer duration of several weeks or months.

Conclusion
The efficacy of amiodarone therapy in preventing recurrence of AF in patients with paroxysmal and persistent AF was not affected by the duration of AF when the boundary of duration for analysis was fixed at 48 h. These results suggest that amiodarone has pharmacological characteristics of multi-channel blockade that is relatively free from the influence of channel modification induced by remodeling.

References
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