Effect of Low-Dose Amiodarone on Atrial Fibrillation or Flutter in Japanese Patients With Heart Failure

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The efficacy and safety of amiodarone in the management of atrial fibrillation (AF) or flutter in 108 Japanese patients with heart failure was retrospectively examined. Thirty-four (41%) of the 82 patients who were in sinus rhythm after 1 month of amiodarone administration had their first recurrence, 70% of cases occurring within 1 year of initiation. The cumulative rates of maintenance of sinus rhythm were 0.68, 0.55, and 0.47 at 1, 3, and 5 years, respectively. Amiodarone was more effective in maintaining sinus rhythm in patients with paroxysmal AF or flutter than in those with the persistent form ($p<0.05$). The cumulative rates for cases that remained in permanent AF were 0.04, 0.11, and 0.14 at 1, 3, and 5 years, respectively. Apart from suppressing AF, the mean heart rate during Holter monitoring was significantly decreased with amiodarone therapy in cases of permanent AF. Adverse effects requiring the discontinuation of amiodarone therapy occurred in 16% of patients. Low-dose amiodarone therapy may prevent AF or flutter in Japanese patients with heart failure. (*Circ J* 2002; 66: 600–604)

Key Words: Amiodarone; Antiarrhythmic drugs; Atrial fibrillation; Atrial flutter; Heart failure

Atrial fibrillation (AF) frequently occurs in patients with congestive heart failure: in one study 22% of 750 heart failure patients with a left ventricular ejection fraction (LVEF) of less than 40% had a history of AF.¹ During the 40 years of follow-up in the Framingham study, 21.8% of male and 28.9% of female subjects with AF developed heart failure, compared with only 3.2% and 3.7%, respectively, of those without AF.² However, there are no reports concerning the incidence of AF or its prognosis in Japanese patients with heart failure.

Atrial fibrillation can lead to clinical deterioration and hospitalization for heart failure;^{3–5} and it also increases the risk of cardiovascular morbidity among patients with a severe heart failure.⁶ Therefore, the prevention or conversion of AF or flutter is important in the management of heart failure. Many class I antiarrhythmic agents convert AF and maintain sinus rhythm (SR) through a slowing of conduction velocity, but may also worsen heart failure through their significant negative inotropic effects^{7–9} and thus increase the risk of death in patients with heart failure.⁷ Randomized control trials for prevention of cardiac death in patients with impaired cardiac function have suggested that amiodarone therapy is suitable for management of AF in patients with heart failure;^{10–14} and it was reported in the recent DIAMOND trial that dofetilide was effective in converting AF, preventing its recurrence, and reducing the risk of hospitalization for worsening heart failure in patients with congestive heart failure and left ventricular dysfunction,

without affecting mortality.¹⁵ Class III antiarrhythmic drugs, such as amiodarone and dofetilide, would thus appear to have significant advantages over class I drugs in patients with AF and heart failure.

Amiodarone is commonly used for ventricular tachyarrhythmia in patients with underlying heart disease, but it is not always used for prevention of atrial tachyarrhythmia in patients with heart failure in Japan. There are few reports concerning the efficacy and safety of antiarrhythmic drug therapy against atrial tachyarrhythmia in Japanese patients with heart failure, so we retrospectively examined the role of amiodarone in the management of AF or flutter.

Methods

Subjects

The study group comprised 108 patients who received amiodarone for refractory arrhythmia at The Heart Institute of Japan, Tokyo Women's Medical University, between February 1988 and January 2001. All patients had AF or flutter and symptomatic heart failure (New York Heart Association (NYHA) functional class II–IV). All patients had underlying heart disease with an impaired left ventricular ejection fraction, estimated to be less than 50% on left ventriculography or radionuclide ventriculography. Informed consent for amiodarone therapy was obtained.

Classification of AF or Flutter

Paroxysmal AF or flutter is characterized by recurrent episodes alternating with SR.¹⁶ Episodes that lasted longer than 2 min and spontaneously reversed within 7 days without antiarrhythmic drug therapy or electrical cardioversion were classified as paroxysmal;¹⁷ and those requiring pharmacological or nonpharmacological cardioversion for termination were classified as persistent.¹⁶ If the condition could not be terminated despite these treatments or if

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Table 1 Baseline Clinical Characteristics

No. of patients	108
Age (years)	55±13
M/F	92/16
Atrial fibrillation or flutter	
Paroxysmal	36 (33%)
Nonparoxysmal	72 (67%)
Ventricular tachycardia or fibrillation	103 (95%)
Underlying heart disease	
Ischemic heart disease	37 (34%)
Idiopathic dilated cardiomyopathy	30 (28%)
Hypertrophic cardiomyopathy	8 (7%)
Arrhythmogenic right ventricular cardiomyopathy	6 (6%)
Valvular disease	11 (10%)
Congenital heart disease	8 (7%)
Others	8 (7%)
NYHA functional class	II 14, III 75, IV 10, V 9
Left ventricular ejection fraction (%)	35±16

± values are mean±SD. Percentage are of patients.

patient did not wish to undergo cardioversion and remained in a state of AF, the case was classified as permanent AF or flutter; that is, labeling a patient as having permanent AF or flutter was an expression of the patient's intent rather than a description of the pathophysiology.¹⁶

Drug Dosing

Patients were loaded with oral amiodarone at a dose of 400–800 mg/day for 7–14 days. In some cases administration was begun at 200 mg/day because of concomitant organic lung disease or reduced diffusing capacity of the lungs. After the initial loading phase, the maintenance dose of 50–200 mg/day was adjusted while the efficacy and side effects were monitored.

Follow-up

All patients were hospitalized for at least 2 weeks while undergoing the initial amiodarone loading and follow-up was continued at 1 month after discharge, and then at intervals of 1–3 months. Baseline 12-lead ECG, echocardiography, Holter monitoring, thyroid and liver function tests, pulmonary function tests, ophthalmologic examination, and chest X-ray were performed for most patients before amiodarone therapy (those requiring emergency care for acute myocardial infarction or severe heart failure did not always undergo Holter monitoring, pulmonary function testing or an ophthalmologic examination). Twelve-lead ECG was performed several times during the initial loading phase and also at each outpatient visit. Holter monitoring, thyroid and liver function testing, pulmonary function testing, and chest X-ray were used to assess the efficacy and adverse effects of amiodarone therapy at week 2, month 1 and 3, and then every 3 months after initiation. Echocardiography and ophthalmologic examination were performed every 6 months.

We confirmed the recurrence of AF or flutter with or without symptoms by ECG at scheduled, unscheduled, or urgent visits, by Holter monitoring or by the recording of a device such as a pacemaker or implanted cardioverter defibrillator. We also investigated the possibility of recurrence when patients complained of typical clinical symptoms.

Statistical Analysis

Summary data are presented either as mean±SD or as

Fig 1. Kaplan-Meier estimates of the proportion of patients with no recurrence of atrial fibrillation or flutter in those with sinus rhythm at baseline or 1 month after initiation of amiodarone (n=82).

numbers of patients. Baseline characteristics were compared between patients with and without recurrence of AF or flutter by either the Mann-Whitney test or Student's t-test. Mean heart rate values during Holter monitoring for each month after initiation of amiodarone therapy were compared with the baseline (before initiation) data by paired Student's t-test. The cumulative rate of recurrence of AF or flutter, and that for cases in permanent AF, were estimated by the product-limit method of Kaplan and Meier, and the differences among the various groups were assessed by the log-rank test. A p value less than 0.05 was considered statistically significant.

Results

Patient Characteristics

In this study, 72 patients (67%) had either persistent or permanent AF or flutter and 36 had paroxysmal AF or flutter; 103 patients (95%) had concomitant sustained or nonsustained ventricular tachycardia or ventricular fibrillation. Ischemic heart diseases accounted for 34% of the underlying heart diseases and nonischemic conditions accounted for 64%. All 8 patients with hypertrophic cardiomyopathy had a history of congestive heart failure, and 7 patients were in the end-stage or dilated phase with concomitant systolic dysfunction.^{18,19} The mean LVEF was 35±16% (Table 1).

Among the patients in this study, 37 (34%) had received class I antiarrhythmic drugs prior to amiodarone therapy and in all but 2 AF or flutter recurred in spite of treatment. Ventricular tachycardia also appeared as a drug-induced proarrhythmia in 2 other cases.

Response to Amiodarone Therapy

During a mean follow-up period of 36±28 months (median: 25; range: 1–123 months), 16 patients died: sudden cardiac death (4 patients), heart failure (6 patients), and noncardiac causes (6 patients).

The basal rhythm at the start of amiodarone therapy (baseline) was found to be AF in 39 patients. Sinus rhythm was successfully restored in 13 patients, including 7 patients by electrical cardioversion, within 1 month after initiation of amiodarone therapy. During the follow-up period, 34 (41%) of the 82 patients who were in SR after 1 month of amiodarone administration had recurrence of AF or flutter. The time to first recurrence ranged from 1 to 28 months after initiation of amiodarone therapy, and 24 patients (71%) experienced their first recurrence within 12 months

Table 2 Clinical Characteristics of Patients With and Without Recurrence of Atrial Fibrillation or Flutter

	With recurrence	Without recurrence	p value
No. of patients	34	48	
Age (years)	55±15	56±16	0.69
M/F	27/7	40/8	0.65
Ischemic heart disease	8 (24%)	22 (46%)	0.03
Left ventricular ejection fraction (%)	37±18	35±16	0.60
Paroxysmal atrial fibrillation or flutter	10 (29%)	26 (54%)	0.03
Maintenance dose of amiodarone (mg/day)	147±67	132±48	0.24
Concomitant drugs			
Diuretics	22 (65%)	36 (75%)	0.32
Digoxin	21 (62%)	17 (35%)	0.02
ACE inhibitors/AT1-blockers	21 (62%)	39 (81%)	0.15
-adrenoceptor antagonists	19 (56%)	22 (46%)	0.08
Antiplatelet drugs	9 (26%)	20 (42%)	0.16
Anticoagulants	22 (65%)	30 (63%)	0.63

± values are mean±SD. Percentage are of patients with or without recurrence. ACE, angiotensin-converting enzyme; AT1, angiotensin II subtype 1.

Fig2. Kaplan-Meier estimates of the proportion of patients with no recurrence of atrial fibrillation or flutter in those with paroxysmal (n=36) vs persistent (n=46) atrial fibrillation or flutter.

Fig3. Kaplan-Meier estimates of the proportion of patients with no recurrence of atrial fibrillation or flutter in those with left atrial diameter (LAD) <45 mm (n=64) vs LAD ≥45 mm (n=18) at baseline.

Fig4. Kaplan-Meier estimates of the probability of permanent atrial fibrillation in patients with sinus rhythm at baseline or 1 month after beginning amiodarone (n=82).

Fig5. Changes in mean heart rate during Holter monitoring in patients with permanent atrial fibrillation before and during amiodarone therapy. Values are expressed as mean±SD. ***p<0.001, **p<0.01, *p<0.05 compared with before.

of initiation. The cumulative rates for maintenance of SR were 0.68, 0.55, and 0.47 at 1, 3, and 5 years, respectively (Fig1). The maintenance dose of amiodarone was not significantly different between patients with and without recurrence. There were lower rates of ischemic heart disease and lower occurrence of paroxysms in patients with recurrence than in those without recurrence (Table2). The cumulative rate of maintenance of SR was significantly higher in patients with paroxysmal AF or flutter than in those with the persistent form ($p<0.05$) (Fig2), and there was a significantly greater rate of recurrence in patients with a left

atrial diameter (LAD) ≥45 mm than in those with a LAD <45 mm ($p<0.01$) (Fig3).

The cumulative rates for cases that remained in permanent AF during amiodarone therapy were 0.04, 0.11, and 0.14 at 1, 3, and 5 years, respectively (Fig4). Permanent AF was found in 26 patients before and during amiodarone therapy and of those, 21 were examined to detect changes in mean heart rate by Holter monitoring within 6 months of

initiating amiodarone therapy. They were also given the same doses of negative chronotropic drugs, such as digoxin and α -adrenoceptor antagonists, during this period and the mean heart rate significantly decreased after initiation of amiodarone therapy (Fig 5).

Side Effects Requiring Discontinuation of Amiodarone

Amiodarone therapy was discontinued in 17 patients (16%): 10 patients had a decrease in the DLco, an indicator of the diffusing capacity of the lung, 3 patients developed pulmonary fibrosis, 1 patient developed hyperthyroidism, 2 patients developed sinus bradyarrhythmia and 1 patient had sustained monomorphic ventricular tachycardia. None of the patients died as a result of the adverse effects associated with amiodarone.

Discussion

Amiodarone is effective in supraventricular arrhythmia as well as ventricular arrhythmia.⁹ The development of AF results in worsening heart failure, causing an uncontrolled heart rate with shortened filling time and provocation of tachycardiomyopathy; absence of the atrial kick and irregular ventricular rhythm will lead to a fall in cardiac output.³ Neurohormonal disturbance will also be induced by activation of the autonomic nervous system and renin-angiotensin system, and will in turn aggravate the heart failure and AF.^{3,4} A recent report indicated that the plasma levels of atrial and brain natriuretic peptides could provide independent prognostic information of the recurrence of AF in patients with mild heart failure.²⁰ There is also a risk of thromboembolism in patients with uncontrolled heart failure who develop AF.⁵ In Japanese patients with AF, underlying heart disease, particularly nonischemic cardiomyopathy, increases the risk of cerebral and peripheral arterial ischemic events.²¹ The maintenance of SR is important in AF in patients with impaired cardiac function resulting from structural heart disease.

Nonrandomized trials showed that the superiority of amiodarone in maintaining SR in cases of refractory AF or flutter in which SR could not be maintained with class I antiarrhythmic drugs;^{22–29} and a recent randomized trial showed that amiodarone is more effective than propafenone and sotalol for the prevention of AF.³⁰ Thirty-seven of the present patients had been given class I antiarrhythmic drugs before the amiodarone therapy trial, but in most cases their AF could not be controlled. Moreover, class I antiarrhythmic drugs are associated with a higher incidence of adverse effects, such as proarrhythmia and conduction disturbances, and thus increase the risk of arrhythmic death or worsening heart failure.^{3,5,7} In the present study, 70% of the patients were administered angiotensin-converting enzyme inhibitor or angiotensin II type 1 receptor blocker as the basic treatment of heart failure and these drugs may also be beneficial in the management of heart failure and AF through their reduction of neurohormonal activation.^{1,3}

Our result of 59% of patients successfully maintaining SR while on low-dose amiodarone during a mean follow-up of 18 months is comparable with the results of previous studies (53–79%).^{22–30} However, unlike the previous studies in which recurrence increased linearly, our results are characterized by the first recurrence most often occurring within 1 year of initiating amiodarone therapy and the reasons for this difference may include: (1) a lower maintenance dose of amiodarone than previously reported (200–400 mg/day);²⁹

(2) symptomatic heart failure and left ventricular dysfunction in all patients in the present study; and (3) many of the present patients had nonischemic heart disease. However, the final maintenance dose in patients without recurrence was 132 ± 48 mg/day (plasma concentrations were 0.54 ± 0.30 μ g/ml for amiodarone and 0.48 ± 0.24 μ g/ml for its active metabolite, desethylamiodarone), which was lower than previously reported;^{28–30} so we believe that the effect of amiodarone may not be simply a matter of the dose-effect relationship during long-term therapy.

In addition, it would appear that amiodarone is effective in maintaining SR as the basal rhythm because the rate of remaining in permanent AF was very low in the present study, even in cases of recurrence. To date, the efficacy of treatment for atrial tachyarrhythmia has been evaluated in clinical trials by comparing the time to the first recurrence; this method may be considerably less able to detect effective treatment than has been supposed.³¹ Previous reports have indicated that 40–50% of cases of heart failure result in sudden cardiac death;^{32,33} but in our study of patients receiving amiodarone, there were only 4 sudden cardiac deaths. Therefore, there is a need for a comprehensive evaluation of the efficacy of amiodarone for the prevention of not only atrial tachyarrhythmia but also sudden cardiac death in patients with heart failure.

Our results demonstrated that amiodarone was more effective in maintaining SR in cases of paroxysmal rather than in persistent AF or flutter, which differs from the results of Chun et al.²⁸ The reason for the greater recurrence rate in patients with persistent AF is not clear, but may be related to the organically stabilized substrate. Atrial enlargement is considered both a cause and a consequence of atrial tachyarrhythmia and in the present study the incidence of recurrence was higher in cases with a large left atrial diameter (≥ 45 mm). Additionally, in terms of atrial stretch, atrial tachyarrhythmia is induced by activation of stretch-activated ion channels;³⁴ which induces abnormal automaticity and triggered activity, slowing of conduction, and increased dispersion of refractoriness.^{3,4,34}

Apart from suppression of AF, amiodarone reduces the ventricular rate in permanent AF^{3,35} and also improves the hemodynamics of patients with rapid AF and heart failure.³⁶ In the present study, the mean heart rate during Holter monitoring before and during amiodarone therapy was significantly decreased within 2 weeks of drug administration and the effect remained after 6 months in cases of permanent AF, and this may play a part in the beneficial effect of long-term amiodarone therapy.

Adverse Effects

The incidence of intolerable noncardiac effects resulting in withdrawal of the drug in low-dose amiodarone therapy for AF has been reported as 1–21%.^{22–30} We did not record any fatal adverse events, but amiodarone was discontinued because of noncardiac effects in 14 cases (13%), a rate similar to that in the other reports.

Study Limitations

This study was retrospective without a control group, and was not always designed to study the protocol for the prevention of atrial tachyarrhythmia. In addition, cardioversion was not performed in all cases showing AF at baseline, and the study lacked objectivity in the definition of permanent AF. Therefore, we cannot make a conclusion about the absolute efficacy of low-dose amiodarone for suppression

of AF.

Conclusion

We retrospectively examined the efficacy and safety of amiodarone in maintaining SR in Japanese patients with AF or flutter and heart failure. It would appear to be effective, with few cardiac side effects, and may also achieve ventricular rate control in cases of permanent AF. Therefore, clinicians can expect that amiodarone therapy for Japanese patients with atrial tachyarrhythmia and concomitant heart failure will be efficacious.

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