Journal of Cardiology (2011) **58**, 108—115

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Original article

Role of oral amiodarone in patients with atrial fibrillation and congestive heart failure

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Received 4 April 2011; received in revised form 16 June 2011; accepted 21 June 2011
Available online 9 August 2011

KEYWORDS
Amiodarone;
Atrial fibrillation;
Heart failure;
B-type natriuretic peptide

Summary
Background: Amiodarone is recognized as the most effective therapy for maintaining sinus rhythm (SR) post cardioversion in patients with atrial fibrillation (AF). It is also recommended for controlling AF in patients with congestive heart failure (CHF). We retrospectively examined the efficacy and safety of oral amiodarone in patients with AF and CHF.
Methods: Forty-eight consecutive AF patients whose left ventricular ejection fraction (LVEF) was less than 50% and B-type natriuretic peptide (BNP) was higher than 100 pg/ml were investigated retrospectively, and divided into 3 groups: paroxysmal AF, 16 patients; persistent AF, 9 patients; and permanent AF, 23 patients.
Results: The permanent AF group had a longer history of AF, larger left ventricular end-diastolic diameter (LVDd) and left atrial diameter (LAD) than paroxysmal and persistent AF groups ($p < 0.05$). After median follow-up of 265 days, amiodarone suppressed paroxysms in 88% of paroxysmal AF patients, while SR was maintained in all persistent AF patients, and 35% of permanent AF patients. Of the 32 persistent and permanent AF patients, 12 (71%) out of 17 maintained SR after successful electrical cardioversion, and conversion to SR occurred spontaneously in 5 (33%) out of 15. The effective group had significantly smaller LVDd and LAD than the ineffective group. In the effective group, BNP decreased significantly from 723 ± 566 pg/ml to 248 ± 252 pg/ml, ($p < 0.0005$) and LVEF increased significantly from $33 \pm 7\%$ to $50 \pm 13\%$ ($p < 0.0005$) during follow up, while no changes were observed in the ineffective group. The patients with low LVEF ($\leq$30%) benefited comparably from amiodarone to the patients with LVEF >30%. Complications occurred in 24 (50%) patients leading to discontinuation of amiodarone in 11 (23%).

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0914-5087/$ — see front matter
doi:10.1016/j.jjcc.2011.06.005

Conclusions: Oral amiodarone helped restore SR in paroxysmal and persistent AF patients with CHF. The successful rhythm control by amiodarone resulted in the improvement of LV function and the decrease of BNP levels.

Introduction

Effective rhythm control of atrial fibrillation (AF) frequently bestows clinically meaningful advantages, such as increased exercise tolerance, improvement in symptoms, and prevention of atrial remodeling. The incidence of AF increases with the onset of congestive heart failure (CHF) and rhythm control is attempted in patients with AF and CHF in practice [1,2].

Amiodarone is recognized as the most effective therapy for maintaining sinus rhythm (SR) post cardioversion. It is also recommended for controlling AF in patients with CHF since it has little negative inotropic action and possibly fewer proarrhythmic effects [3].

There are many reports about the effects of amiodarone in AF patients with CHF from western countries [4—17], indicating that it is effective in restoration and maintenance of SR in those patients. However, there are few reports from Japan [18]. The principal purpose of this retrospective study was to evaluate the efficacy and safety of oral amiodarone in Japanese patients with AF and CHF for clinical use, which would be meaningful in their management.

Methods

This study retrospectively investigated a total of 48 consecutive AF patients (39 men and 9 women, mean age 66 ± 10 years) treated with oral amiodarone between January 2004 and December 2008. All patients had symptomatic CHF [New York Heart Association (NYHA) functional classes II—IV] and their B-type natriuretic peptide (BNP) was higher than 100 pg/ml. All patients had underlying heart disease with an impaired left ventricular ejection fraction (LVEF) less than 50% on echocardiography.

Inpatients underwent continuous electrocardiographic (ECG) monitoring. At the outpatient clinic follow-up was performed at least every 3 months. ECGs and a 24-h Holter ECG were recorded regularly or when patients complained of palpitation or other typical clinical symptoms. The efficacy of amiodarone therapy was assessed by using ECG, Holter monitoring, or the recording of a pacemaker. In order to assess adverse effects of amiodarone, spirometry, chest X-ray, KL-6 level, thyroid hormones, and liver function were checked. We checked clinical and demographic data, including past medical history and prior medication, from medical records. Follow-up was terminated in April 2009.

Definitions

We recognized three categories: (1) Paroxysmal AF, defined as recurrent, self-terminating episodes of AF usually lasting <48 h, alternating with periods of SR; (2) Persistent AF, defined as episodes of sustained AF that did not convert to SR spontaneously, but required pharmacological or electrical cardioversion; (3) Permanent AF, defined as continuous AF, in which cardioversion had not been attempted or had been unsuccessful, and in which AF was accepted as the long-term rhythm for that patient [3].

Treatment was considered effective when the duration and frequency of episodes of AF were suppressed in paroxysmal AF, or when SR was maintained in persistent and permanent AF. The recurrence of AF was defined as any recording of AF on an ECG or 24-h Holter monitoring.

Statistical methods

All data are expressed as mean $\pm$ SD or numbers and percentages of patients. Data were censored if the patient discontinued amiodarone, reached the end of the follow-up period (April 2009), or was lost to follow-up. Differences in continuous variables were analyzed with unpaired Student's *t*-test or ANOVA and Tukey post-hoc tests. The *G*-test was used to test for independence in contingency tables. A value of $p < 0.05$ was considered statistically significant. The survival curve illustrating freedom from recurrence of AF and the curve for spontaneous conversion were assessed by the Kaplan—Meier method. SPSS version 11.0.1 was used for all statistical analyses.

Results

There were 16 patients in the paroxysmal AF group, 9 in the persistent AF group, and 23 in the permanent AF group. The median follow-up duration was 265 days (range 7—1920, average 378 days). Amiodarone was started after effective anticoagulation therapy in all patients. The mean dose of amiodarone was 163 ± 80 mg/day (range 50—400 mg/day). Twenty-three patients discontinued amiodarone because of a lack of efficacy or adverse effects. The underlying heart diseases included ischemic heart disease 18, hypertensive heart disease 10, valvular disease 7, idiopathic dilated cardiomyopathy 5, tachycardia-induced cardiomyopathy 4, congenital heart disease 2, arrhythmogenic right ventricular cardiomyopathy (ARVC) 1, and sarcoidosis 1.

The baseline characteristics of the patients are shown in Table 1. The three AF groups differed in age ($p < 0.05$), duration of history of AF ($p < 0.05$), left ventricular end-diastolic diameter (LVDd; $p < 0.005$), and left atrial diameter (LAD; $p < 0.05$). In post-hoc comparisons, the mean age of the paroxysmal AF group was significantly higher compared with the other 2 groups. The permanent AF group had a significantly longer duration of AF and larger left atrium and ventricle compared with the other 2 groups.

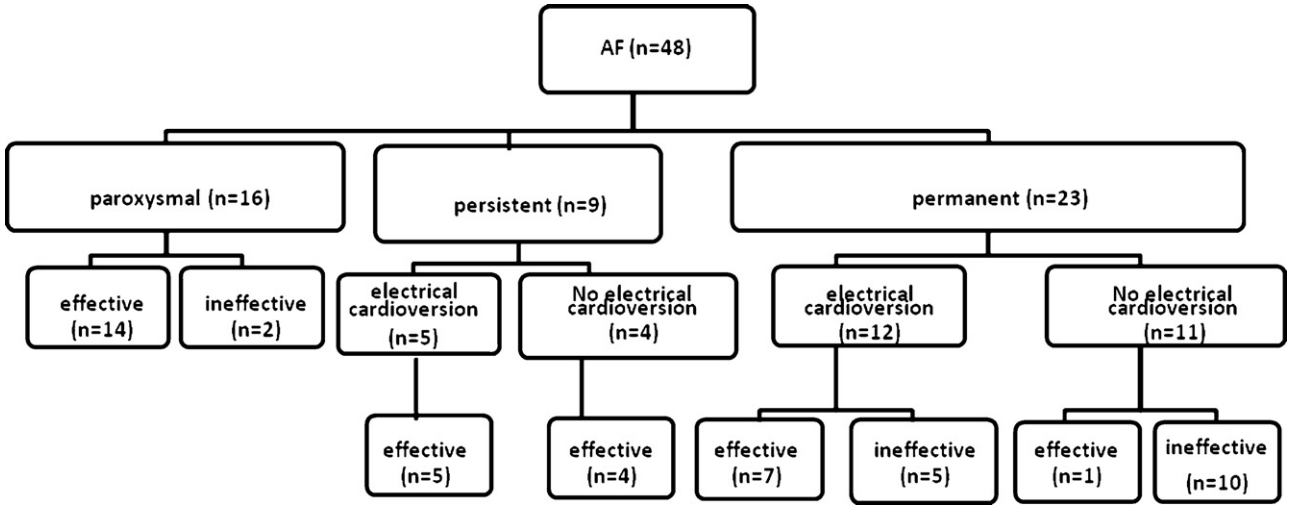

Figure 1 Tree diagram showing results of treatment with oral amiodarone. AF, atrial fibrillation.

Tallying the results for patients who had never received cardioversion, amiodarone suppressed AF in 14/16 of the paroxysmal AF patients (88%), and caused spontaneous reversion to SR in 4/4 persistent AF patients (100%), and 1/11 permanent AF patients (9%) (Fig. 1). This translated to the spontaneous achievement of SR in 5/15 non-paroxysmal AF patients (33%) without cardioversion after a median follow-up of 151 days. The time to attainment of SR was within 4 months (mean 40 days) (Fig. 2). Meanwhile, 17 patients (5 in the persistent and 12 in the permanent AF group) received electrical cardioversion. AF did not recur in any of the 5 persistent AF patients (100%), and 7/12 permanent AF patients (58%), translating to SR maintenance in 12/17 (71%) patients receiving cardioversion with a median follow-up of 216 days. Recurrence of AF among treatment failures was within 1 month with a median length of 16 days (Fig. 2). In total, amiodarone was effective in 100% and 35% of the persistent and permanent AF patients, respectively. Among 14 patients who had previously failed to cardiovert with other antiarrhythmic agents (range, 1—7 agents), amiodarone was effective in 9.

In the ineffective group ($n = 17$), LVDd and LAD were significantly longer compared with the effective group ($n = 31$) (Table 2). The BNP level was significantly higher in the effective group. There was no significant difference in the maintenance dose of amiodarone between the groups. These results were the same in the non-paroxysmal patients ($n = 32$). LVDd and LAD were significantly longer in the ineffective group ($n = 15$) compared with the effective group ($n = 17$) (LVDd 67 ± 9 mm vs. 56 ± 10 mm; $p < 0.005$; LAD 53 ± 7 mm vs. 44 ± 7 mm; $p < 0.005$). There were no significant differences in the age, gender, duration of AF, or the maintenance dose of amiodarone between the groups.

In the amiodarone-effective group, BNP decreased significantly from 723 ± 566 pg/ml to 248 ± 252 pg/ml ($p < 0.0005$) and LVEF increased significantly from $33 \pm 7\%$ to $50 \pm 13\%$ ($p < 0.0005$) during the follow-up period, while no changes were observed in the ineffective group. There were no changes in LVDd or LAD during the observation period in

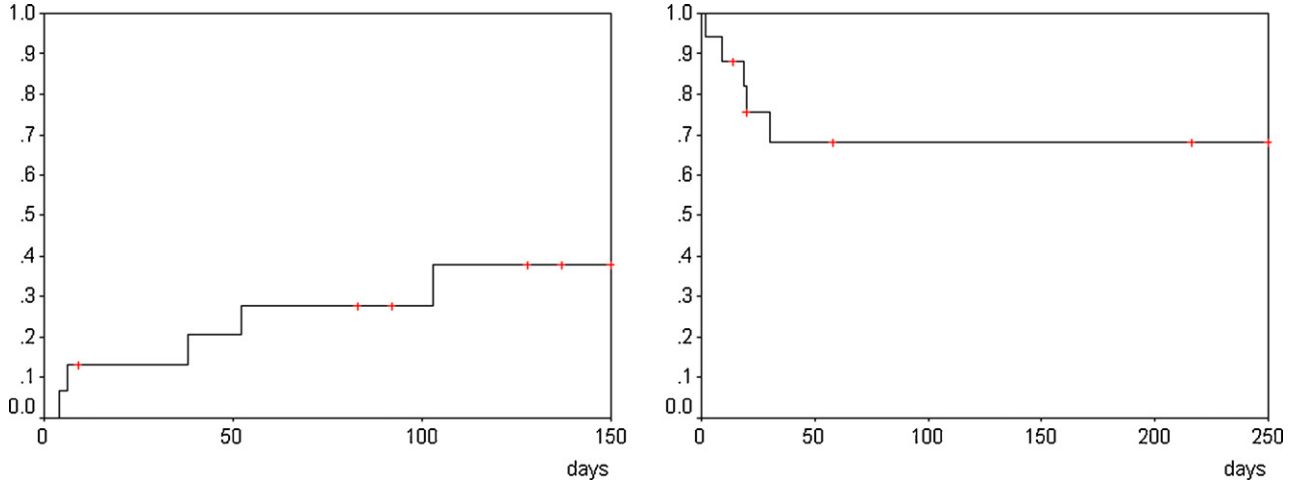

Figure 2 Left panel shows the Kaplan—Meier analysis of spontaneous conversion to sinus rhythm after treatment with amiodarone in non-paroxysmal atrial fibrillation (AF) patients. Right panel shows the event-free Kaplan—Meier curve with no recurrence of AF after cardioversion in non-paroxysmal AF patients.

Table 1 Baseline characteristics of the patients.

	Paroxysmal ($n=16$)	Persistent ($n=9$)	Permanent ($n=23$)	Significance*
Age (years)	71 ± 6**	61 ± 14	65 ± 9	$p=0.047$
Male (%)	69	78	91	N.S.
Duration of AF (days)	941 ± 1610	96 ± 238	3068 ± 3994[a]	$p=0.021$
NYHA class (II/III/IV)	9/6/1	7/2/0	20/3/0	N.S.
BNP(pg/ml)	928 ± 899	733 ± 483	499 ± 386	N.S.
LVEF (%)	36 ± 9	34 ± 6	35 ± 7	N.S.
LVDd (mm)	53 ± 9	53 ± 10	65 ± 9[a]	$p=0.004$
LAD (mm)	41 ± 7	42 ± 5	51 ± 8[a]	$p=0.009$
Previous drug failures (%)	50	11[b]	22	$p=0.0012$
Ablation (isthmus) (%)	0	11	9	N.S.
Medication				
Beta-blockers (%)	44	56	74	$p=0.10$
ACEi/ARB (%)	50	56	70	N.S.
Digitalis (%)	25	22	17	N.S.
Verapamil (%)	50	22	26	N.S.
Other antiarrhythmic agents (%)	13	11	13	N.S.
Statins (%)	19	22	17	N.S.
Hypertension (%)	56	56	74	N.S.
Diabetes mellitus (%)	44	33	35	N.S.

$\pm$ Values are mean $\pm$ SD.
ACEi, angiotensin-converting enzyme inhibitor; AF, atrial fibrillation; ARB, angiotensin II receptor blocker; BNP, B-type natriuretic peptide; LAD, left atrial diameter; LVDd, left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; PVI, pulmonary vein isolation.
* p values ≤ 0.1 are given, although significance was defined at the 0.05 level.
** Statistically significant difference vs. both persistent and permanent atrial fibrillation.
[a] vs. both paroxysmal and persistent atrial fibrillation.
[b] vs. both paroxysmal and permanent atrial fibrillation.

Table 2 Clinical characteristics of effective and ineffective patients.

	Effective ($n=31$)	Ineffective ($n=17$)	p value
Age (years)	65 ± 11	67 ± 7	N.S.
Male (%)	75	94	0.092
Duration of AF (days)	581 ± 756	3470 ± 4877	0.055
BNP (pg/ml)	806 ± 725	468 ± 354	0.036
NYHA class (II/III/IV)	22/8/1	14/3/0	N.S.
LVEF (%)	34 ± 7	36 ± 9	N.S.
LVDd (mm)	55 ± 10	65 ± 11	0.002
LAD (mm)	43 ± 7	53 ± 7	0.001
Previous drug failures (%)	29	29	N.S.
Ablation (isthmus) (%)	10	0	N.S.
Dose of amiodarone (mg)	148 ± 52	188 ± 112	N.S.
Follow-up duration (days)	393 ± 349	350 ± 490	N.S.
Medication			
Beta-blockers (%)	61	59	N.S.
ACEi/ARB (%)	61	59	N.S.
Digitalis (%)	23	18	N.S.
Verapamil (%)	35	29	N.S.
Other antiarrhythmic agents (%)	13	12	N.S.
Statins (%)	23	12	N.S.
Hypertension (%)	58	76	N.S.
Diabetes mellitus (%)	39	35	N.S.

ACEi, angiotensin-converting enzyme inhibitor; AF, atrial fibrillation; ARB, angiotensin II receptor blocker; BNP, B-type natriuretic peptide; LAD, left atrial diameter; LVDd, left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association.

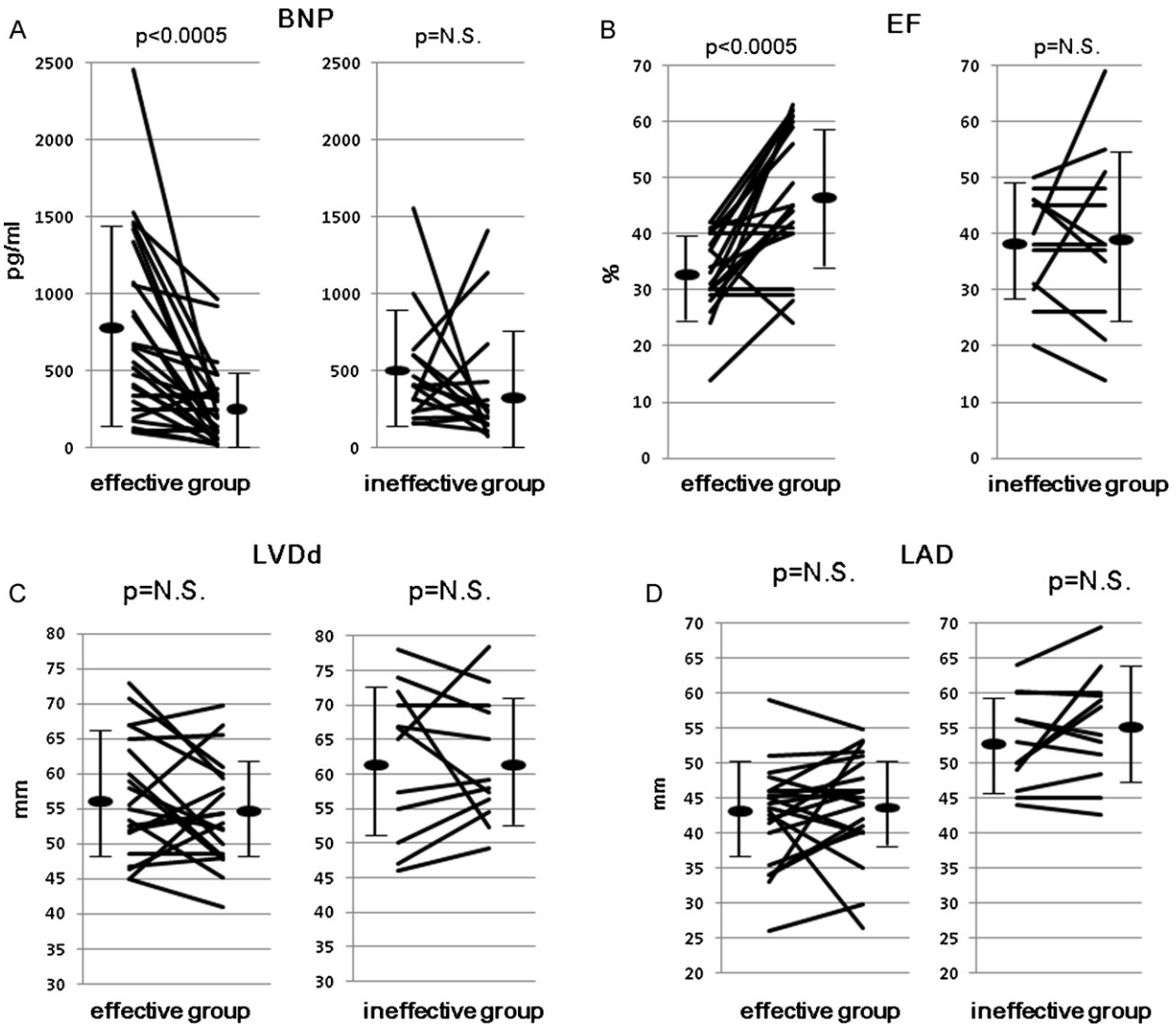

Figure 3 Effects of amiodarone treatment on clinical indices grouped by success or failure of rhythm control. Left side points show pre-treatment values in individual patients, and the right side shows values after treatment. Amiodarone significantly improved BNP levels and EF after the follow-up period compared with that at baseline in the effective group, but not in the ineffective group. BNP, B-type natriuretic peptide; EF, left ventricular ejection fraction; LVDd, left ventricular end-diastolic diameter; LAD, left atrial diameter.

either group (Fig. 3). During the follow-up period, 5 patients were admitted because of exacerbation of CHF. They consisted of 1 persistent and 4 permanent AF patients. There was no significant difference in the ratio of admission due to deterioration of CHF between the amiodarone-effective and -ineffective groups (2/31, 6% vs. 3/17, 18%). One paroxysmal AF patient with ARVC started amiodarone during the hospitalization because of deteriorated CHF. Although the attacks of AF were suppressed, CHF progressed and she died.

There were 16 patients with low LVEF ($\leq$30%); 7 patients in paroxysmal AF, 5 patients in persistent AF, and 4 patients in permanent AF ($p = 0.73$). There were no significant differences in the BNP levels, LVDd, or LAD between the patients with LVEF $\leq$30% and those with LVEF >30% (BNP 847 ± 775 pg/ml vs. 606 ± 550 pg/ml; LVDd 60 ± 9 mm vs. 58 ± 12 mm; LAD 44 ± 7 mm vs. 47 ± 9 mm). Amiodarone was effective in 11/16 LVEF $\leq$30% group, and in 20/32 LVEF >30% group ($p = 0.46$).

Over the course of the follow-up period, adverse effects occurred in 24 (50%) patients. Recorded adverse effects were bradycardia in 7 (15%), thyroid dysfunction (all hypothyroidism) in 10 (21%), pulmonary events in 8 (17%), excessive QT prolongation (QTc > 0.52) in 3 (6%), and liver dysfunction in 1 (2%). Amiodarone was discontinued in 11 (23%) of these patients (thyroid dysfunction 3, pulmonary events 7, and liver dysfunction 1). In the remaining 13, amiodarone dosage was decreased, or treatment for thyroid dysfunction was initiated. Among 7 patients who showed bradycardia, 5 had sinus bradycardia of 40—60 BPM and in the other 2 patients sick sinus syndrome was revealed and pacemakers were implanted. The most common non-cardiac adverse events responsible for discontinuation were pulmonary abnormalities including an increase in serum KL-6 levels. Only 1 patient was diagnosed with interstitial pneumonia. Although amiodarone-induced pulmonary toxicity is difficult to prove, the main cause of the pulmonary injury

Table 3 Clinical characteristics of patients with or without adverse effects.

	With adverse effects ($n=24$)	Without adverse effects ($n=24$)	p value
Age (years)	68 ± 9	64 ± 10	N.S.
Male (%)	75	88	N.S.
Duration of AF (days)	1759 ± 3842	1196 ± 1689	N.S.
BNP (pg/ml)	493 ± 381	879 ± 778	0.036
NYHA class (II/III/IV)	18/5/1	18/6/0	N.S.
LVEF (%)	37 ± 7	33 ± 7	0.042
LVDd (mm)	59 ± 11	59 ± 11	N.S.
LAD (mm)	46 ± 10	46 ± 7	N.S.
Dose of amiodarone (mg)	160 ± 91	165 ± 70	N.S.
Follow-up duration (days)	457 ± 494	299 ± 263	N.S.
Medication			
Beta-blockers (%)	54	67	N.S.
ACEi/ARB (%)	63	58	N.S.
Digitalis (%)	25	17	N.S.
Verapamil (%)	33	33	N.S.
Other antiarrhythmic agents (%)	9	17	N.S.
Statins (%)	17	21	N.S.
Hypertension (%)	67	63	N.S.
Diabetes mellitus (%)	38	38	N.S.

ACEi, angiotensin-converting enzyme inhibitor; AF, atrial fibrillation; ARB, angiotensin II receptor blocker; BNP, B-type natriuretic peptide; LAD, left atrial diameter; LVDd, left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association.

was suspected to be hypersensitivity pneumonitis in that patient. The median duration from the start of amiodarone to the appearance of complications was 94 days (range 6—1751 days). Proarrhythmic effects were not seen in any patients. There were no significant differences in age, dose of amiodarone, or other medication between the patients with and without adverse effects (Table 3). Those with side effects had significantly lower BNP level and higher LVEF compared with those without side effects.

Discussion

This study was a retrospective assessment of the efficacy and safety of oral amiodarone for the suppression of AF in patients with CHF. Amiodarone was effective in 88%, 100%, and 35% of the paroxysmal, persistent, and permanent AF patients, respectively. In non-paroxysmal AF patients, oral administration of amiodarone maintained SR after direct-current shocks in 71% after 216 days and was associated with a spontaneous cardioversion rate of 33% after 151 days. The amiodarone-effective group had significantly smaller left atrium and ventricle than the ineffective group. Restoration and maintenance of SR significantly improved LVEF and decreased BNP. The patients with LVEF $\leq$30% benefited from amiodarone comparably to those with LVEF >30%. Adverse effects arose in 50% patients, resulting in discontinuation of amiodarone in about half of them.

Management of patients with non-paroxysmal AF and CHF

Amiodarione is currently the most effective prophylactic drug for the maintenance of SR in patients with AF who undergo cardioversion. There are various reports on the efficacy of amiodarone in maintaining SR after cardioversion and on spontaneous cardioversion rates in patients with non-paroxysmal AF. In the literature, the prevention of recurrence of AF after cardioversion ranges from 44% to 67% after follow-up of 8 weeks to 3 years [4—12]. In patients not receiving cardioversion, administration of oral amiodarone is associated with a conversion rate between 12% and 83% over 28 days [6—11,13—15]. Conflicting results among trials probably reflect differences in dosing and loading protocols in trials, differing duration of AF prior to treatment, and follow-up periods.

The significance of various factors in predicting AF free interval in chronic AF and CHF patients after electrical cardioversion varies among previous reports [16]. In the present study, predictive factors for both preservation of SR after cardioversion and spontaneous conversion were left atrial and ventricular size. Clinical parameters such as age, gender, duration of AF, and underlying cardiac disease did not affect the outcome. Amiodarone was less effective in AF patients with advanced anatomical remodeling in our study.

AF is highly common in CHF patients and its incidence increases with advancing CHF. On the other hand, AF with an uncontrolled rapid and irregular ventricular response may aggravate CHF. Na channel blockers in patients with AF in the setting of CHF are associated with an increased risk of potentially fatal proarrhythmia or aggravation of CHF caused by negative inotropic effects [19], while amiodarone is recommended in such patients because of its lower proarrhythmic potential and lack of significant negative inotropic effect in CHF [3]. According to previous reports, spontaneous conversion to SR due to amiodarone in permanent AF with CHF was seen in 31% of patients after 4 years [17]. The mean maintenance dose of amiodarone in our study was lower compared

to that in this study. The presence of systolic LV dysfunction did not significantly affect the outcome, indicating the utility of amiodarone for controlling AF in patients with CHF.

Clinical advantage of successful rhythm control of AF

In patients with AF, the restoration and maintenance of SR is a desirable goal. AFFIRM demonstrated no significant differences in incidence of stroke, quality of life, or mortality with rhythm vs. rate control [20]. In the AF-CHF study there was no difference in cardiovascular death between the rate control and rhythm control groups in the patients with AF and CHF [21]. However, amiodarone can improve cardiac function and relieve symptoms by prevention of AF recurrence [22]. In the current report, significant improvement in LVEF and BNP levels was observed in the effective patients, although no significant reverse remodeling occurred as assessed by LA and LV dimensions. We hypothesize that the improvement in LVEF and BNP may have been due in part to reversal of tachycardia-induced cardiomyopathy by rate control due to other concomitant drugs and rhythm control by amiodarone. The lack of improvement in LA and LV dimensions may have been due to irreversible structural changes. On the other hand, in the ineffective group no changes were observed in the mean of LVEF or BNP levels during the follow-up. However, there was a minority whose LVEF and BNP levels were improved. Oral amiodarone failed in rhythm control although its effects on rate control would cause such results in those patients [3].

Adverse effects

All antiarrhythmic agents have the potential for serious adverse events, which are seen more commonly in patients with left ventricular dysfunction, CHF, or ischemic heart disease [23,24]. The proportion of patients who discontinued taking amiodarone because of adverse events in our study (23%) was similar to that reported in other large trials [17,22] and a report from Japan [18]. In our series, amiodarone was prescribed prudently with frequent check-ups and discontinued immediately if any suspicion of side effects appeared. We also attempted to switch amiodarone to less toxic antiarrhythmic drugs if LV function improved. Therefore, although the proportion of side effects was quite high, there were no serious events. In this report patients with adverse effects had better LVEF compared with those without adverse effects. It may be one of the causes that we followed the patients with more impaired LV function more carefully. We concluded that amiodarone was generally well tolerated when used with caution.

Amiodarone was usually started with the recommended loading dose of 400 mg, and reduced to the maintenance dose of 50—200 mg in individual patients. Both the loading and maintenance doses were adjusted due to patients' age, heart rate, body weight, the clinical states, and so on. In this report the mean dose of amiodarone was the last dose which the patient was given. Some patients discontinued taking amiodarone because of adverse events during the loading period with the dose of 400 mg, which made the mean dose higher than other Japanese report [18].

Limitations

Because this was a retrospective study, it had some limitations. There was no definite protocol and management decisions were made by individual physicians. Therefore, the dose of amiodarone, the indication for cardioversion, the method of dealing with adverse effects, and use of other drugs were not uniform. The treatment was adjusted within the limits of clinical judgment and patient tolerance. Thus, our results likely reflect what most experienced physicians would do in clinical practice. Prospective studies in a large number of patients with AF and CHF in Japan are needed to evaluate the therapeutic value of amiodarone.

It has been demonstrated that BNP and proBNP levels can facilitate diagnosis and guide CHF therapy [25]. In this report we defined CHF patients as those whose BNP was higher than 100 pg/ml. While some researchers state values of >100 pg/ml indicate CHF, others suggest a value of >200 pg/ml. On the other hand, there are some conditions other than CHF associated with elevated BNP levels, including LV hypertrophy, tachycardia, right ventricular overload, myocardial ischaemia, hypoxaemia, renal dysfunction, advanced age, liver cirrhosis, sepsis, and infection [26]. In some patients BNP might be elevated because of rapid ventricular response during AF.

The maintenance of SR after cardioversion or reversion to SR may not be solely attributable to antiarrhythmic properties of amiodarone. Improvement of CHF and the effects of up-stream treatment by angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers would also support SR maintenance [27]. It is hard to distinguish between amiodarone effect and other factors.

Finally, the median follow-up duration of 265 days was not so long.

Conclusion

Oral amiodarone had clinical value in restoration and maintenance of SR in CHF patients with paroxysmal and persistent AF. The successful rhythm control resulted in the improvement of LVEF and the decrease in BNP levels. However, its utility appeared to be limited in those with advanced atrial anatomical remodeling of patients with CHF.

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