Obesity Is Associated With the Development of Interstitial Pneumonia Under Long-Term Administration of Amiodarone in Refractory Atrial Fibrillation Patients

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SUMMARY

Although oral amiodarone (AMD) has been used for the management of atrial fibrillation (AF), serious complications such as interstitial pneumonia (IP) occur very occasionally. We evaluated which factors were associated with the development of IP under the long-term administration of AMD in patients with refractory AF.

This study included 122 consecutive patients (65.8 ± 11.4 years, mean body mass index [BMI] of 23.2 ± 4.3 kg/m^2) who orally received AMD to inhibit AF between January 2004 and December 2013. Administration of AMD was begun at 400 mg daily as a loading dose, and was continued at a dosage of 50-400 mg daily after the initial loading phase, determined by the control of the arrhythmias and occurrence of side-effects. The clinical factors were compared between the patients with and without adverse effects, especially IP.

During an average follow-up period of 49.2 ± 28.2 months, 53 patients (43.4%) were determined to have converted and maintained sinus rhythm. In contrast, adverse effects were detected in 46 patients (37.7%) with AMD. IP occurred in 8 patients (6.6%), thyrotoxicosis in 35 (28.7%), and others in 5 (4.1%). Four (50.0%) out of 8 patients complicated with IP had obesity (BMI > 27 kg/m^2). Among the clinical factors, only obesity was significantly associated with the development of IP ($P = 0.026$).

In patients with refractory AF, AMD had an antiarrhythmic effect with long-term administration, but greater adverse effects were also observed. Obesity was the most significant factor associated with the development of IP. (Int Heart J 2016; 57: 30-34)

Key words: Adverse effects, Lung injury, Mono-desethylamiodarone, Body mass index, Toxicity

Amiodarone (AMD) is classified as a class III antiarrhythmic drug according to the Vaughan Williams classification. Further, AMD has many pharmacological effects in addition to its potassium channel blocker effect, such as calcium channel blocker, sodium channel blocker, and sympathetic inhibitory actions. It also has a high distribution in fatty tissue and a long half-life. Mono-desethylamiodarone, a metabolite of AMD (M-AMD), also possesses pharmacological activity equivalent to that of AMD. Oral AMD is effective for refractory atrial fibrillation (AF).[1-5] Although serious lung injury such as interstitial pneumonia (IP) occasionally occurs (10%), the mortality rate is 2%.[2,6] In recent years, the administration of AMD has increased in AF patients, and serious complications such as interstitial pneumonia (IP) occasionally occur. Therefore, we evaluated which factors were associated with the development of IP under long-term administration of AMD in patients with refractory AF.

METHODS

Study population: Among 294 consecutive patients who were orally administered AMD between January 2004 and December 2013 at our institute, 122 (41.5%) with AF were included in this retrospectively study. The patients had either a paroxysmal or persistent pattern of AF. The clinical characteristics of the patients are outlined in Table I.

AF therapy and amiodarone: After defining the anticoagulation therapy, a rate control or rhythm control strategy was chosen as the AF management. The clinical decision to use a rhythm or rate control strategy needed to consider several factors, including the degree of the symptoms, presence of comorbidities, and likelihood of a successful cardioversion. AMD is often used for long-standing AF that other antiarrhythmic drugs are not effective for or to consider the patient's cardiac function. Further, as a hybrid therapy, with electrical cardioversion or catheter ablation of AF, AMD is administered to main-

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Table I. Patient Backgrounds

AF patients administered AMD, $n = 122$	
Male, number (%)	99 (81.1)
Age (years)	65.8 ± 11.4
BMI (kg/m^2)	23.2 ± 4.3
DM, number (%)	40 (32.8)
CKD, number (%)	44 (36.1)
CHF, number (%)	88 (72.1)
ICD, number (%)	31 (25.4)
HT, number (%)	54 (44.3)
Stroke, number (%)	7 (0.1)
$CHADS_2$ score (0/1/2/3/4/5)	7/37/52/19/5/2
Drug dose (mg)	182.6 ± 62.4
Serum concentration of AMD (μg/mL)	0.94 ± 0.50
Serum concentration of M-AMD (μg/mL)	0.68 ± 0.28
Administration term (months)	15.5 ± 20.8 (7.2)
Follow up term (months)	49.2 ± 28.2 (39.1)

AF indicates atrial fibrillation; AMD, amiodarone; BMI, body mass index; DM, diabetes mellitus; CKD, chronic kidney disease; CHF, chronic heart failure; ICD, ischemic cardiac disease; HT, hypertension; AMD, amiodarone; and M-AMD, metabolites of amiodarone. Data are expressed as the mean ± SD, number (%), and the median.

tain sinus rhythm.[7]

Amiodarone administration protocol: The AMD therapy was administered in a loading and maintenance dose phase. The administration of AMD was begun at 400 mg daily for 14 days as a loading dose, and AMD was continued at a dosage of 50 - 400 mg daily after the initial loading phase, determined by whether or not it controlled the arrhythmia and the occurrence of side effects. However, some patients were given 200 or 300 mg daily because of concomitant lung disease or heart failure. The plasma concentration of AMD and metabolites of AMD (M-AMD) were measured by high performance liquid-chromatography every 3-6 months, and a 12-lead electrocardiogram (ECG) was also performed during the follow-up.

Diagnosis of IP: As the diagnosis of IP, the patients met the following criteria: 1) the patients had a new onset of pulmonary symptoms such as dyspnea, a cough, and a fever; 2) new chest radiographic abnormalities, and ground glass opacity (GGO), appearing on the chest radiography or computed tomography (CT) scan; 3) elevated serum KL-6 level (KL-6 > 500 U/mL); and 4) congestive heart failure, infections, and malignancy were ruled out.[8]

Follow-up of the pulmonary side effects: To monitor the presence of pulmonary toxicity, the serum KL-6 level and chest radiography were checked every 3 months during the first year and then every 6-12 months during the AMD therapy. Additional testing was performed if pulmonary toxicity was suspected, such as with the presence of a cough, fever, and dyspnea. During the follow-up period, the detection of pulmonary toxicity prompted us to stop the AMD therapy. Further, we changed to other antiarrhythmic drugs or considered catheter ablation.

Serum KL-6 was determined using an enzyme immunoassay kit or electrochemiluminescence immunoassay kit.

Follow-up of other side effects: Generally other side effects such as thyroid dysfunction or hepatic disorders occasionally occurred. Therefore, the usual blood tests (including AST/ALT), serum TSH, free-T3, and free-T4 were also checked every 3-6 months during the AMD therapy. Serum free-T3 and free-T4 were determined with chemiluminescence assay kits. Serum TSH was determined with immunoradiometric assay kits. The presence of eye symptoms was also checked by a medical examination every follow-up visit.

Statistical analysis: All continuous data are expressed as the mean ± standard deviation, median (quartile: 25% - 75%), or number (%). Comparisons between groups were analyzed using a univariate analysis (Unpaired *t*-test, Fisher's exact test, and Mann-Whitney test) and multivariate analysis using a Cox proportional hazard model. The relationship of the administration of AMD and the IP complication rate was analyzed using the Kaplan-Meier method, and the curves were compared using a log-rank test. A P value < 0.05 was considered statistically significant. The statistical analyses were performed using R commander version 1.24 software.[9]

Ethical considerations: This study was approved by our institutional review board (number 27-13).

All patients provided informed consent for the study protocol that was approved by the institutional review boards.

Results

Baseline characteristics: The mean age was 65.8 ± 11.4 years old, 99 (81.1%) were men, and the body mass index (BMI) was 23.2 ± 4.3 kg/m^2. The $CHADS_2$ Score was 0, 1, 2, 3, 4, and 5 in 7, 37, 52, 19, 5, and 2 of the 122 AF patients, respectively. The mean AMD dose was 182.6 ± 62.4 mg, and the mean duration of administration was 49.2 ± 28.2 months. Fifty-three patients (43.4%) were determined to have converted and were maintained in sinus rhythm. In contrast, adverse effects (mild - severe) were detected in 46 patients (37.7%). IP was seen in 8 patients, thyrotoxicosis in 35, drug eruptions in one, bradycardia in 3, and an extended QT in one (Figure 1). The baseline characteristics are listed in Table I.

Incidence and prognosis of IP: Of the 122 patients, IP was seen in 8 patients (6.6%). The 8 patients with IP are listed in Table II. On the CT scans, abnormalities were found in 4 patients. In all patients the administration of AMD was stopped, and two patients were treated with corticosteroids at a dose equivalent to 0.5 - 1.0 mg/kg/day of prednisolone (PSL), and one patient was treated with a corticosteroid-plus therapy. The IP improved in all patients and they could be discharged. We divided the 122 patients into two groups; an IP group and non-IP group, and the clinical factors were compared between the patients with and without IP.

Risk factors of IP: When comparing the IP and non-IP groups, the mean BMI (23.0 ± 4.2 kg/m^2 [non-IP group] versus 26.4 ± 4.9 kg/m^2 [IP group]; $P = 0.029$) was significantly higher in the IP group than in the non-IP group (Table III). Among the clinical factors, only obesity was a significant factor for the development of IP ($P = 0.026$) (Table IV). Since the BMI in the IP group was 26.4 ± 4.9 kg/m^2, we decided the cut-off value of the BMI should be 27 kg/m^2, and divided the patients into two groups, a BMI > 27 kg/m^2 group and BMI < 27 kg/m^2 group. The complication rate of the occurrence of IP was compared between the BMI > 27 kg/m^2 group and BMI < 27 kg/m^2 group by a Kaplan-Meier survival curve, and the rates differed significantly ($P = 0.013$) (Figure 2). An ROC curve comparing the BMI and IP showed that the cut-off value of the BMI was 27.2 kg/m^2 (AUC 0.69; 95% confidence interval: 0.51 - 0.88)

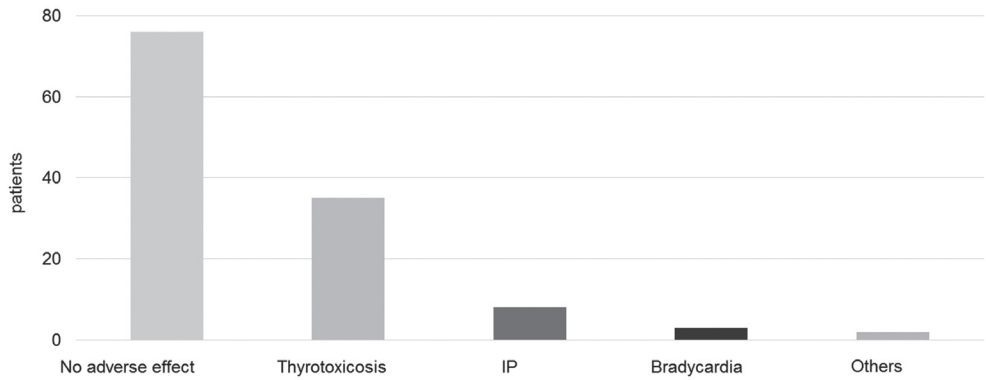

Figure 1. Adverse effects of amiodarone. Adverse effects were detected in 46 patients (37.7%). IP indicates interstitial pneumonia. IP was seen in 8 patients, thyrotoxicosis in 35, a rash from the drug in one, bradycardia in 3, and an extended QT interval in one.

Table II. Patients With Interstitial Pneumonia

No	Age (years)	Sex	Height (cm)	Weight (kg)	Dose (mg)	Duration (months)	EF (%)	LAD length/wide (cm)	Cr (mg/dL)	AMD (μg/mL)	M-AMD (μg/mL)	KL-6 (U/mL)	TSH (μU/mL)	F-T3 (pg/mL)	F-T4 (ng/mL)	Xp/CT pattern
1	53	M	166.5	80.4	200	6.1	61.3	5.83/5.07	1.1	0.85	0.71	797	3.25	2.76	1.49	WNL
2	70	M	158.0	75.0	200	8.0	57.9	6.17/4.76	0.8	0.84	0.60	1058	2.65	1.28	2.76	ARDS
3	81	F	152.4	49.6	50	29.5	21.7	7.16/5.58	0.9	0.22	0.25	822	3.62	2.45	1.24	WNL
4	67	M	162.6	93.4	200	6.0	32.3	6.35/4.86	2.0	0.79	0.27	1040	5.78	1.69	1.98	NSIP
5	75	M	160.3	64.0	200	3.1	38.1	5.89/3.05	0.8	1.02	0.88	227	0.99	1.73	2.21	NSIP
6	68	M	166.4	61.2	100	12.4	40.4	5.48/4.89	2.4	0.37	0.28	843	3.01	2.64	1.48	WNL
7	69	M	170.0	62.0	200	1.9	44.6	5.32/4.22	0.9	0.52	0.37	796	19.8	3.29	1.10	WNL
8	84	M	158.0	68.0	200	13.4	63.4	7.37/5.93	1.0	0.43	0.55	1130	42.5	1.81	0.65	NSIP

EF indicates ejection fraction; LAD, left atrial dimension; AMD, amiodarone; M-AMD; metabolites of amiodarone; WNL, within normal limits; ARDS, acute respiratory distress syndrome; and NSIP, non-specific interstitial pneumonia. Data are expressed as the mean ± SD, numbers (%), and the median.

Table III. Comparison of the Patient Characteristics Between the IP and Non-IP Groups

	Non-IP (n = 114)	IP (n = 8)	P
Male, number (%)	92 (80.7)	7 (87.5)	0.99*
Age (years)	65.5 ± 11.6	69.9 ± 8.3	0.30*
BMI (kg/m^2)	23.0 ± 4.2	26.4 ± 4.9	0.029*
CHADS$_2$ score (0/1/2/3/4/5)	7/35/48/18/4/2	0/2/4/1/1/0	0.47***
Drug dose (mg)	183.6 ± 62.8	168.8 ± 59.4	0.52*
Serum concentration of AMD (μg/mL)	1.00 ± 0.51	0.63 ± 0.28	0.054*
Serum concentration of M-AMD (μg/mL)	0.72 ± 0.36	0.49 ± 0.23	0.084*
Administration term (months)	15.8 ± 21.4	11.1 ± 9.8	0.54***
Antiarrhythmic effects of AMD, number (%)	47 (41.2)	6 (75.0)	0.077**

BMI indicates body mass index; AMD, amiodarone; M-AMD, metabolites of amiodarone. Data are expressed as the mean ± SD or number (%). P values were determined by *unpaired t-test, **Fisher's exact test, and ***Mann-Whitney test.

Table IV. Predictors of IP Detected by Cox Proportional Hazard Model

Variable	Univariable analysis		Multivariable analysis	
	OR (95%CI)	P	OR (95%CI)	P
Age > 65 years	6.45 (0.79-298.91)	0.069	5.18 (0.63-42.26)	0.12
BMI > 27 kg/m^2	5.23 (0.89-30.88)	0.035	4.55 (1.14-18.21)	0.032
CHADS$_2$ score > 2	1.74 (0.29-18.40)	0.71	1.19 (0.23-6.13)	0.84
M-AMD > 0.68 μg/mL	0.60 (0.056-3.53)	0.71	0.24 (0.043-1.31)	0.10

OR indicates odds ratio; and CI, confidential interval.

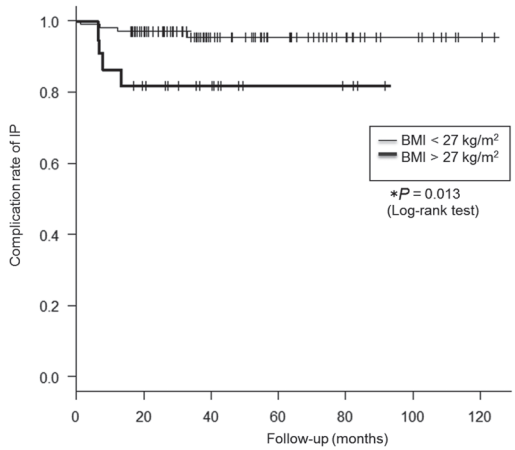

Figure 2. Kaplan-Meier curve regarding IP complications. Comparison between the patients with a BMI of < 27 kg/m^2 and BMI of > 27 kg/m^2. The IP complication rate differed significantly in the log-rank test.

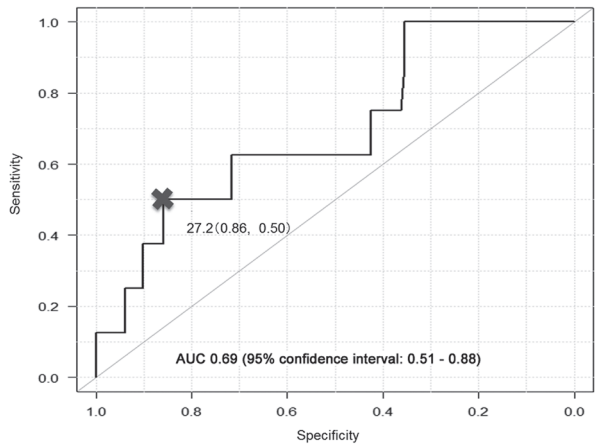

Figure 3. ROC curve between the BMI and IP. An ROC curve between the BMI and IP revealed that the BMI cut-off was 27.2 kg/m^2 (AUC 0.69; 95% confidence interval: 0.51 - 0.88).

(Figure 3). On the other hand, there was no significant difference between thyrotoxicosis and BMI.

Discussion

Main findings: Obesity was the most significant risk factor associated with the development of IP in the long-term follow-up study. In particular, the cutoff point of BMI as a predictor of IP was 27 kg/m^2.

Pharmacokinetics and adverse effects of AMD: After the oral administration of AMD, the blood concentration rises dose-dependently and AMD is distributed into tissue, especially fat, the skin, and lungs.[10] AMD is metabolized to mono-N-desethylamiodarone by deiodination, dealkylation, and glucuronic acid conjugation, and then it is excreted into the bile.[11] The adverse effects of AMD are recognized as thyrotoxicosis, liver injury, corneal deposits, and pulmonary injury. It is reported that serious lung injury occurs in 5-10% of patients administered AMD.[6,10] In the 1980s, high doses of AMD were identified as causing the development of IP.[12] In the 1990s, some reports showed that generally, low-dose therapy is safer.[13,14] However, a recent report concluded that IP could occur with low-dose AMD therapy at a daily dose of 200 mg.[15]

Mechanisms of the adverse effects of AMD: The mechanism of thyrotoxicosis due to AMD has been elucidated. AMD inhibits the conversion of the enzyme triiodomthyronine to thyroxine in peripheral tissues. Further, the synthesis and secretion of the thyroid hormone is suppressed by an iodine excess, which AMD has (Wolff-Chaikoff effect). Hyperthyroidism due to AMD is a destructive thyroiditis. There is no fixed relationship with the dose of AMD in hyperthyroidism caused by AMD.[16] Even if it occurs, hyperthyroidism is often cured within a few months.

On the other hand, the mechanisms of the lung injury due to AMD remain uncertain, but some reports have suggested possible mechanisms; the direct toxicity of AMD and indirect effects such as an immune-mediated hypersensitivity-based mechanism.[17] It was recently suggested that alveolar macrophages are given a crucial toxicity by metabolites containing a diethylaminoethoxy group, such as mono-desethylamiodarone.[18,19] In the lung tissue or bronchoalveolar lavage (BAL) of IP patients administered AMD, many inflammatory cells such as monocytes, macrophages, and polynuclear cells are recognized.[20]

Association between the development of IP and BMI: AMD and mono-desethylamiodarone have a large distribution volume and long elimination half-life, so they accumulate in peripheral tissues for long periods.[10] Long-term administration of AMD tends to increase the risk of developing IP. It was suggested that the direct toxic effect of drug accumulation, especially of mono-desethylamiodarone, is associated with lung injury.[18,21,22] The etiology of IP occurring in the early phase may not be from the direct toxic effect as that occurring in the late phase. It might be associated with an allergic reaction, rather than a direct toxic action.[2,21] Since AMD is a lipid soluble drug, there is the possibility that it accumulates in obese patients and causes adverse effects.

It has been reported that obesity affects the pharmacokinetics of AMD, and a high BMI decreases the clearance of AMD.[23] It was reported that the dose of AMD, age (> 65 years), and BMI (> 25 kg/m^2) were variable factors for the clearance of AMD.

The age, dose of AMD, and serum concentration of AMD were associated with the development of IP in several reports.[6,15] We considered the reasons why these factors were not risk factors for AMD-induced IP in our study.

Firstly, we investigated the development of IP under the long-term administration of AMD in patients with refractory AF. In patients with refractory AF, especially elderly patients, it is difficult to eliminate AF by administering AMD, and these patients stop receiving AMD early before developing side effects. Therefore, age may not be a variable factor for the development of IP.

Secondly, we tended to avoid the long-term administration of high dose AMD, because it is well-known that high dose AMD and a high concentration of AMD are risk factors for IP. As a result, the dose or serum concentration of AMD was not associated with the development of IP. Although the serum concentration of AMD was low, AMD accumulated in

adipose tissue.

In conclusion, because AMD exists in adipose tissue during the mono-desethylamiodarone state, there is more mono-desethylamiodarone in obese patients than in normal body weight patients. However, little has been reported indicating that obesity is directly related to the development of IP.

It is difficult to eliminate AF in obese patients so these patients often tend to be administered AMD for the long-term. Therefore, it is important for them to lose weight in order to prevent AF or the development of IP.

Obesity and BMI: The World Health Organization recommends a BMI cutoff point of 30 kg/m^2 for obesity. This cutoff point was derived largely from mortality statistics from European and American populations. On the other hand, Asian people are smaller than Europeans and Americans. Several studies have separately reported that the BMI cutoff point for obesity for Asian populations was pegged between 23 and 27 kg/m^2.[24-27] In our study, a BMI of > 27 kg/m^2 was defined as obesity based on these studies.[24]

Study limitations: This study had some potential limitations. It was a retrospective and observational study conducted at a single institute. There were only a few cases with IP in this study, which might have caused a statistical bias. Further research is necessary with more cases.

Conclusions: IP mostly occurred within one year from the first administration of AMD. There were no significant differences in the age, dose of AMD, and length of the administration of AMD between the IP and Non-IP groups. Obesity (BMI > 27 kg/m^2) was the only independent and significant predictor of IP.

Disclosures

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