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Efficacy and Safety of Low Dose Amiodarone for Management of Tachyarrhythmias in Japanese Patients

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KAWANO ET AL.: Efficacy and Safety of Low Dose Amiodarone for Management of Tachyarrhythmias in Japanese Patients. Background: The major concern during amiodarone (AMD) therapy is the adverse effects including pulmonary toxicity. However, low dose AMD may reduce the side effects without loss of anti-arrhythmic efficacy. The aim of this study is to investigate the efficacy and safety of low dose AMD therapy for tachyarrhythmias.

Methods and Results: AMD was given in 84 patients (60 males, mean age 66 years) with atrial and/or ventricular tachyarrhythmias and left ventricular dysfunction (mean ejection fraction: 0.26 ± 0.12). The major underlying diseases were ischemic heart disease (36) and dilated cardiomyopathy (27). Mean follow-up period was 15 ± 14.1 months. Oral AMD was initially loaded 400 mg daily for 3 days and then maintained between 50 to 200 mg daily. Follow-up examination was performed before and after oral AMD at 1, 3, 6 and every 6 months. Efficacies for arrhythmias were evaluated by symptoms, standard 12-leads ECG, and ambulatory ECG. Mean initial dose was 200 ± 106.8 mg and maintenance dose was 100 ± 62.6 mg daily. During follow-up period, targeted tachyarrhythmias were successfully suppressed in 66 (78.6%) of 84 patients. Adverse effects were observed in 16 patients (19.0%); thyroid dysfunction (11.9%), liver dysfunction (2.4%), pulmonary toxicity, finger tremor, hypogeusia and sinus bradycardia, respectively (1.2%). Pulmonary toxicity was not lethal and no progression was observed with reducing use of AMD.

Conclusion: Low dose AMD therapy was effective for suppression of tachyarrhythmias with impaired cardiac function and safely administered with few serious complications. (J HK Coll Cardiol 2009;17:19-26)

Adverse effects, amiodarone, low dose administration

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EFFICACY AND SAFETY OF LOW DOSE AMIODARONE

Introduction

Amiodarone (AMD) is known to be effective for atrial fibrillation (AF), atrial flutter (AFL), and ventricular tachyarrhythmias (ventricular tachycardia: VT, ventricular fibrillation: VF). It could be administered to patients with cardiac dysfunction because of less negative inotropic and proarrhythmic effects. However, the adverse effects including pulmonary toxicity are always major concern.

In previous studies in Western countries, it has been reported that low dose AMD therapy was well tolerated and maintained long-term suppression of arrhythmias. Besides, it may reduce the risk of adverse complications. However, in Japanese patient population, no study has been conducted whether the appropriate lower dose of AMD could be effective and safe or not.

We hypothesized that appropriate low dose AMD therapy for Japanese patients may be effective and also reduce the incidence of adverse effects. We evaluated retrospectively the clinical efficacy and safety of lower dose AMD therapy in patients with tachyarrhythmias and cardiac dysfunction.

Methods

Study Subjects (Table 1)

Eighty-four patients (60 male, 24 female, mean age 66±13.0 year old) with VT, VF, AF, and AFL were enrolled in this study. All patients had cardiac dysfunction and the mean left ventricular ejection fraction (LVEF) measured by 2D-echocardiography was 0.26±0.12. Mean follow-up period was 15±14.1 months ranging 6 to 71 months. In this series, 36 patients had ischemic heart disease (IHD) and 48 patients had non-ischemic heart disease (NIHD). In NIHD group, there were 27 dilated cardiomyopathy (DCM), 4 state after myocarditis, 3 hypertrophic cardiomyopathy, 3 cardiac sarcoidosis, and others (Fabry disease, mitral regurgitation, tachycardia induced cardiomyopathy, and unknown). VT were observed in 70 patients with 40 sustained, 30 non sustained, and VF in 3, AF in 14, AFL in 2. There were 5 patients overlapping VT and AF.

Combination Drugs

Beta blocker were used in 44 patients (52.4%), angiotensin-converting enzyme inhibitors (ACE-I) in 40 (47.6%), angiotensin II receptor blocker (ARB) in 23 (27.4%), digitalis in 38 (45.2%). These drugs had already been administered before the initiation of AMD or simultaneously in some patient.

Study Design

In Western countries, it is recommended that initial dose of oral AMD is 600 to 800 mg daily over 1 week (occasionally, it exceeds 1000 mg daily) and maintenance is 200 mg daily. Also, in our country, initial dose of oral AMD is recommended as 400 mg daily for 2 weeks and maintenance dose is recommended as 200 mg daily. In this study, oral AMD was loaded with initial dose of 400 mg daily for 3 days and then maintained 50 to 200 mg daily. The minimal dose was

Table 1. Characteristics of Patients

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>84</td>
</tr>
<tr>
<td>Male</td>
<td>60</td>
</tr>
<tr>
<td>Age (years)</td>
<td>66±13</td>
</tr>
<tr>
<td>EF</td>
<td>0.26±0.12</td>
</tr>
<tr>
<td>Follow-up (range) (months)</td>
<td>15±14 (6-71)</td>
</tr>
<tr>
<td>Underlying heart disease</td>
<td></td>
</tr>
<tr>
<td>Ischemic HD</td>
<td>36</td>
</tr>
<tr>
<td>Non-ischemic HD</td>
<td>48</td>
</tr>
<tr>
<td>Arrhythmias</td>
<td></td>
</tr>
<tr>
<td>VT/VF</td>
<td>73</td>
</tr>
<tr>
<td>AF</td>
<td>14 (5 overlap with VT)</td>
</tr>
<tr>
<td>AFL</td>
<td>2</td>
</tr>
<tr>
<td>Combination drugs</td>
<td></td>
</tr>
<tr>
<td>Beta blocker</td>
<td>44</td>
</tr>
<tr>
<td>ACE-I</td>
<td>40</td>
</tr>
<tr>
<td>ARB</td>
<td>23</td>
</tr>
</tbody>
</table>

ACE-I: angiotensin converting enzyme inhibitor; AF: atrial fibrillation; AFL: atrial flutter; ARB: angiotensin II receptor blocker; EF: ejection fraction; HD: heart disease; VF: ventricular fibrillation; VT: ventricular tachycardia.
defined as the effective maintenance dose. In some cases (non sustained VT with low incidence and stable hemodynamic state, AF and AFL), maintenance dose was started without initial loading. Mean initial loading dose was 200±106.8 mg and maintenance dose was 100±62.6 mg daily. Standard 12 leads ECG, ambulatory ECG, Chest X-P and computed tomography (CT), echocardiography, and ophthalmologic examination were performed before and after administration of oral AMD at 1, 3, 6 and every 6 months. Complete blood cell counts, biochemistry and thyroid function, serum concentration of AMD, dysethyl-amiodarone (DEA), KL-6, and brain naturiuretic polypeptide (BNP) were also measured.

The efficacy for tachyarrhythmias was evaluated by clinical symptoms and the results of repeated ambulatory ECG. In selected cases with sustained VT, after obtained written informed consent and, the efficacy was evaluated by electrophysiologic study performed at 4 weeks after administration of AMD. The efficacy was actually defined as success in suppression for arrhythmias without increase of the maintenance dose (maximum 200 mg daily) of AMD, and without any additional combination of anti-arrhythmic drugs. If the complete suppression for sustained VT/ VF, more than 50% reduction of non-sustained VT or the elimination of consecutive ventricular premature complexes were recognized, AMD was considered to be effective. Moreover, in patients with implantable cardioverter defibrillator (ICD), even if the cycle length of VT prolonged after initiation of AMD and VT could be terminated by anti-tachycardia pacing without cardioversion, AMD was considered to be effective.

**Results**

**Anti-arrhythmic Efficacy of Low Dose AMD Therapy (Figures 1 & 2)**

In total 84 patients, low dose AMD was given in 73 patients with 30 non-sustained and 40 sustained VT or 3 VF. In 55 (75.3%) of them, it effectively suppressed those arrhythmias. An effective ratio in non sustained and sustained VT had no difference with 76.7% and 72.5%. Also, in the comparison with 29 IHD and 44 NIHD, it was a little higher in IHD (82.7%) than NIHD (70.5%), but there was no adverse effect.

In patients that did not respond to low dose AMD, there were 4 adverse effects (22.2%): liver dysfunction, neurological toxicity, and gastrointestinal effects. No efficacy was recorded in 2 patients (11.1%), who required discontinuation of AMD therapy. AMD dose was increased to ≥200 mg/day in 5 patients (27.8%), and additional combination drugs were required for 7 patients (38.9%).

![Figure 1. Efficacy of low dose AMD for tachyarrhythmias.](image)

![Figure 2. Non-responders to low dose AMD therapy.](image)
significan difference. In 12 of 55 patients, ICD was required simultaneously with initiation of AMD for preventing sudden cardiac death. No recurrences ofVF were observed after administration of AMD. In 4 of 12 patients with ICD, sustained VT was recognized but they were terminated by anti-tachycardia pacing without cardioversion.

Low dose AMD was also given in 14 patients with persistent AF and 2 patients with persistent AFL. Persistent AF or AFL was defined to last for 48 hours or more. Electrical cardioversion was performed in patients with long lasting AF or AFL (>3 months) after treatment of AMD. Although 5 patients with AF and 2 with AFL were performed electrical cardioversion, 9 out of 14 AF spontaneously restored to sinus rhythm within a month after administration of AMD. During follow-up period, sinus rhythm was maintained and there was no recurrence of AF and AFL. Eventually the anti-arrhythmic efficacy by our protocol was rated to 78.6%.

Finally, 18 patients were judged as no efficacy in our protocol. AMD was discontinued in 6 patients because of adverse effects in 4 and no efficacy in 2. Five patients with maintenance dose of 100 mg daily have required increasing the dose up to 200 mg or more, and 7 patients were needed additional combination drugs (6 mexiletine, 1 aprindine).

**Adverse Effects**

Adverse effects were observed in 16 out of 84 patients (19.0%); pulmonary toxicity in 1, thyrotoxicosis in 1, hypothyroidism in 9, liver dysfunction in 2, neurological toxicity in 1, gastrointestinal adverse effect in 1, and sinus bradycardia in 1.

Non-lethal pulmonary toxicity was observed in a 68-year-old male patients. He had DCM with left ventricular EF of 0.25 and non-sustained VT. AMD was initially loaded 400 mg daily for 3 days and then maintained 200 mg daily according to the protocol. Subsequently, non-sustained VT was successfully suppressed and there were no respiratory symptoms. No significant changes in serum concentration of KL-6, AMD, and DEA were observed. However, patchy interstitial infiltration was recognized on 1-year follow-up of chest X-P and CT. Serum concentration of KL-6 concomitantly increased to 737 pg/ml (normal range: <500 pg/ml). This pulmonary toxicity was not lethal, and after reduction of AMD to 100 mg daily, neither progression nor recurrence of arrhythmia was noted.

Thyroid dysfunction was the most prevalent side effects and it was recognized in 10 of those 16 patients. In this study, thyroid dysfunction was defined as state that serum thyroid stimulating hormone (TSH) level was more than 10.0 µIU/ml or less than 0.01 µIU/ml (normal range: 0.56-4.3), and as that the patients required any medication with some symptoms due to thyroid dysfunction. Thyrotoxicosis was observed in a 24-year-old female patient of chronic myocarditis with non-sustained VT (LVEF: 0.3). Initial dose of AMD was 200 mg daily for 3 days and maintenance dose was 100 mg daily. Two years later, serum level of TSH was less than 0.1 µU/ml and serum level free T3, free T4 was elevated and asymptomatic thyrotoxicosis was recognized. Serum concentration of AMD and DEA was not elevated. Approximately 6 months after reduction of AMD to 50 mg daily, thyroid function was developed hypothyroidism without medication and then gradually restored to euthyroid state. Hypothyroidism was recognized in 9 patients with mean follow-up period of 12.9 months after administration of AMD. Patients with hypothyroidism had no symptoms and after maintenance dose reduction or supplement with L-thyroxine, no progression had noted and none of them was discontinued AMD.

Liver dysfunction was observed in 2 patients whose aminotransferase rose above 300 IU/l within 1 week after initiation of AMD. Finger tremor and hypogeusia was recognized in each 1 patients at 1 month and 17 months after administration of AMD, respectively. However, these adverse complications gradually improved after discontinuation of AMD. Sinus bradycardia required implantation of pacemaker was observed at 3 months after treatment. Corneal micro-deposits related the AMD were observed in almost patients, but no visual disturbances were found. There were no dermatologic adverse effects.

No difference was observed between atrial and ventricular tachyarrhythmias or IHD and NIHD on the safety by low dose AMD.
Serum Concentration of AMD, DEA, KL-6, Thyroid Hormones, and BNP

Mean serum concentration of AMD and DEA had been rising for 3 months after administration and then leveled off. Mean concentration at 2 years were 505±273.6 ng/ml, 331±134.9 ng/ml, respectively. In 5 of 84 patients, serum concentration of AMD rose above 1000 ng/ml at 3 months (maximum value: 1687 ng/ml). In these patients, 3 were female, and there were no significant difference in initial and maintenance dose and combination drugs compare to other patients. One female patient had primary biliary cirrhosis, and it was considered as a cause of highly elevated serum concentration of AMD.

During follow-up period, mean serum concentration of KL-6 didn’t increase more than 500 pg/ml except with 2 patients. One of these 2 patients had pulmonary toxicity, and after reduction of AMD, KL-6 was normalized.

Regarding with the thyroid toxicity, average TSH level increased gradually with time course, but it was transient and decreased after 18 months. Free T$_3$ and T$_4$ had not significantly changed. Mean serum concentration of BNP decreased from 348±434.9 to 154±497.5 pg/ml within 1 month after administration of AMD and then the level was maintained in almost patients.

ECG Parameters and Cardiac Function

ECG measurement values such as PR interval, QRS duration and QT interval had no significant changes. RR interval was increased from 0.72±0.20 sec to 0.92±0.12 sec for 6 months after initiation and then leveled off. Baseline mean LVEF on echocardiography was 0.26±0.11. Individual LVEF was 0.25±0.12 in sustained VT, 0.27±0.10 in non-sustained VT, 0.3±0.2 in VF, and 0.32±0.14 in AF, AFL. Also, it was 0.32±0.11 in IHD, 0.21±0.11 in NIHD, 0.29±0.12 in effective group and 0.20±0.11 in non-effective group, respectively. No significant changes of LVEF were observed during follow-up period.

Prognosis

During follow-up period, we lost 17 patients because of heart failure in 14, bacterial pneumonia, colon cancer and suicide in 1, respectively. Further details of 14 patients with heart failure, there were 11 NIHD and 3 IHD. LVEF was not different in both groups (0.24±0.12 vs 0.24±0.10). Cardiac resynchronization therapy was performed in 6 of 14 patients with intractable or drug-refractory heart failure. There were no sudden cardiac death and no death as a result of the adverse effects associated with AMD.

Discussion

AMD is the leading anti-arrhythmic drug, which highly effective for suppression and prevention of arrhythmias, however, the adverse effects including pulmonary toxicity are always major concern. The previous and recent studies revealed that low dose AMD could be effectively applied without serious complication.5-14

In this study, the dose of AMD is set much lower than those reported conventional dosage. The results suggest that the appropriate low dose AMD in our protocol is acceptably effective and safe.

The Efficacy of Low Dose AMD Therapy

Low dose AMD successfully suppressed 75.3% of VT and VF (72.5% of sustained VT, 76.7% of non-sustained VT and 100% of VF), 100% of AF and AFL in this study and favorable results were obtained although the increase of the serum concentration of AMD and DEA was gradual. From the perspective of IHD and NIHD, the efficacy in IHD (82.7%) was a little higher than the one in NIHD (70.5%), but no significant difference was observed. In this study, several reasons were considered why low dose AMD was effective.

The first reason is beta-blocking action of AMD, which indirectly affects the electrophysiologic properties of myocardium. Unlike the standard beta-blocking drugs, the blocking action of AMD to the beta-adrenergic receptors is noncompetitive and additive. It results from inhibition of adenylate cyclase formation and from a reduction in the number of beta-adrenergic receptors.16

The second one is the interactive and synergistic
Efficacy and Safety of Low Dose Amiodarone

Effect with combination drugs, ACE-I, ARB and standard beta-blockers. Approximately 70% of patients were started ACE-I or ARB and 50% were started with beta-blocker before or at the same time of AMD administration. Particularly, AMD combined with beta-blocker was effective for ventricular tachycardia and prevention of arrhythmic death.\(^1\)\(^7\)\(^8\) Although some studies reported the effectiveness for AF by combination of AMD with ACE-I or ARB, no studies showed the efficacy for ventricular arrhythmias with such combinations.\(^1\)\(^9\)\(^2\)\(^0\) Considering the effect of ACE-I or ARB inhibited on sudden cardiac death,\(^2\)\(^1\)\(^2\) it seemed that AMD combined with these drugs was much effective for lethal arrhythmias.

The third one is pharmacokinetic characteristics of AMD. AMD is quite lipophilic and it may account for the unusual pharmacokinetic feature. Usually, AMD is known to slowly distribute to the tissues because of incompletely absorption when oral administration was made. It results in a requirement of very long loading periods, up to several months, before reaching steady-state tissue concentration. Besides AMD is taken up very extensively by tissue, with marked inter-individual variation.\(^2\)\(^1\)\(^4\)

During long-term therapy, an effect of DEA, the metabolite of AMD, also increases like the mother drug and the effect of AMD becomes more complicated. It has been shown that the amount of DEA accumulated in the myocardium after several weeks of initiation of oral AMD is comparable to, or greater than, that of AMD. Also there is a species difference in the extent of myocardial accumulation of DEA.\(^2\)\(^3\)

Electrophysiologically, it has been shown that the effects of oral AMD on sinoatrial and AV nodal function are maximal within 2 weeks, whereas the effects on VT and ventricular refractoriness tend to emerge more gradually, becoming maximal over than 10 weeks.\(^1\)\(^4\) In our study, the effects on ventricular arrhythmias seemed to develop within 1-2 weeks after oral AMD. Theoretically, this is controversial results and further interpretation might be done that AMD and DEA distribute myocardium and give anti-arrhythmic effects before reaching steady-state serum concentration.

The fourth reason is that the patients could keep the inactive state by admission. All patients treated with AMD were required to hospitalization and they have to be keeping rest. Therefore, the relief of physical or mental stresses possibly reduce the incidence of tachyarrhythmias nevertheless the insufficient distribution of AMD to myocardial tissue.

The fifth reason is the amelioration of heart failure. In patients with acute heart failure, the treatment started concomitantly with loading low dose of AMD. It is possible that the improvement of acute heart failure contributed to sufficient reduction of arrhythmias. As the final reason, a racial difference to AMD sensitivity might be considered. Although no studies were conducted about a relation between AMD and racial difference, we may take it into account because even much lower dose AMD than previous reports was effective. Thus, we thought that the acute and partly chronic effects of low dose AMD were contributed to synergistic effects of beta-blocking action, the interactive and synergistic effects with combination drugs, keeping inactive state, a treatment for heart failure or racial difference on AMD sensitivity.

The Safety of Low Dose AMD Therapy

Adverse effects were observed in 16 (19.0%) out of 84 patients in this study.

In detail, we had experienced pulmonary toxicity in one patient (1.2%), hypothyroidism in 9 patients (10.7%), thyrotoxicosis in 1 patient (1.2%). The incidence of pulmonary toxicity has been reported to be about 6% to 8%.\(^2\)\(^4\)\(^2\)\(^5\) It was lower than previous studies in our protocol. Pulmonary toxicity is, however, the most considerable adverse effect. It has been reported that mild to fatal pulmonary toxicity such as adult respiratory distress syndrome can occur even with low dose AMD therapy.\(^2\)\(^6\) In our study, non-lethal pulmonary toxicity occurred one year after
administration of AMD and after reduction of AMD, neither progression of pulmonary fibrosis nor recurrence of arrhythmias was recognized.

The incidence of hyper- or hypothyroidism is reported approximately 2% to 13% and 6 to 13%, respectively.\textsuperscript{27,28} It was equivalent to these studies despite of our appropriate lower dose protocol. In one study, most Japanese patients with AMD induced thyrotoxicosis exhibit type 2 hyperthyroidism.\textsuperscript{29} This type 2 AMD induced thyrotoxicosis is known to occur in the apparently normal thyroid, and results from a direct toxic effect of the drug on the thyroid tissue. It is often difficult to predict the onset of type 2 thyrotoxicosis because it may develop at anytime during treatment with AMD causing destructive thyroiditis with leakage of stored thyroid hormones into the circulation.\textsuperscript{27} On the other hand, AMD induced hypothyroidism was usually not clinical concern because none of those patients discontinued AMD through the reduction of AMD or the supplement with L-thyroxine.

Liver dysfunction is also common adverse complication with AMD. Elevation of serum aminotrasferase is generally noted in 25% of patients on long-term treatment.\textsuperscript{30} In this study, we experienced liver dysfunction in 2 patients within 1 week after initiation of AMD. These cases had no underlying disease, except for heart disease. We speculated that the mechanism of acute liver dysfunction might be idiosyncratic sensitivity to AMD.

Even in those cases with adverse effects, no significant changes in serum concentration of AMD and DEA were observed and no serious complications were developed during follow-up period in this study. However, the incidence of adverse effects increased over time, and adverse effects may be related to the total amount of AMD accumulation. Many of the minor adverse effects are reported to be dose-related, but serious toxicity is often unrelated to the dose and is unpredictable. Regular laboratory examination can help the detection of potential problems and the abnormal findings can be observed preceded to the development of clinical symptoms.\textsuperscript{2} It has been reported that high-resolution CT used in prone positions as well as a supine position could be an effective technique for preventing the clinically serious pulmonary toxicity by AMD.\textsuperscript{31} Therefore, to prevent the serious adverse complication in patients with long-term AMD treatment, routine screening of organic toxicity is very important.

**Study Limitations**

The result of this study must be carefully interpreted because the study was done in non-randomized and retrospective fashion, and sample size and follow-up period were not enough. Particularly the cumulative dose of AMD play an important role for the cause of adverse effect; therefore, we should always pay attention to the potential adverse effects during long-term follow-up period.

**Conclusion**

Appropriate low dose AMD for tachyarrhythmias was effectively administered with few adverse complications. However, careful observation during long-term follow-up is mandatory for the detection of unpredictable complications.

**References**

Efficacy and Safety of Low Dose Amiodarine


