Incidence and Predictors of Pulmonary Toxicity in Japanese Patients Receiving Low-Dose Amiodarone

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**Background** Amiodarone-induced pulmonary toxicity (APT) is the most serious side-effect of amiodarone, and its detection and prevention are extremely important. This study was designed to evaluate the incidence and clinical risk factors of APT, and the utility of a pulmonary function test or serum KL-6 assay to predict pulmonary toxicity in Japanese patients receiving low-dose amiodarone.

**Methods and Results** Five hundred consecutive patients receiving amiodarone were retrospectively evaluated. Mean follow-up period was 48 months and mean maintenance dose was 141 mg daily. Cumulative incidence of APT was 4.2%, 7.8%, and 10.6% at 1, 3, and 5 years, respectively. On multivariate analysis, age at the start (hazard ratio (HR) = 1.48, 95% confidence interval (CI) 1.13 to 1.93) was a significant pretreatment risk factor. Age (HR = 1.64, 95% CI 1.29 to 2.09), maintenance dose (HR = 1.90, 95% CI 1.45 to 2.49) and plasma monodeethylamiodarone concentration (HR = 1.30, 95% CI 1.08 to 1.58) were risk factors. Sensitivity and specificity in screening with measurement of percent predicted diffusion capacity of carbon monoxide, ≥15% individual decrease, were 68% and 69%, and for ≥20% individual decrease, were 59% and 74%, whereas those in screening with serum KL-6 assay, ≥2000 U/ml, were 25% and 91%, respectively.

**Conclusions** Even at low dose, amiodarone shows substantial pulmonary toxicity. Higher age and higher maintenance dose are risk factors. Further decreasing the maintenance dose of amiodarone should be considered in order to reduce the incidence of pulmonary toxicity, at least in Japanese patients. (Circ J 2007; 71: 1610–1616)

**Key Words:** Amiodarone; Carbon monoxide; Diffusion capacity; KL-6; Pulmonary; Toxicity

Amiodarone is a highly effective antiarrhythmic agent for treatment of supraventricular and ventricular tachyarrhythmias. However, its use is limited by several adverse reactions, including cardiac and noncardiac events. Of these, amiodarone-induced pulmonary toxicity (APT) is the most serious and potentially fatal side-effect, and the main reason why physicians have hesitated to use this drug. Early detection of APT is important to prevent a tragic outcome. In the 1980s in the United States, the development of APT was found to be related to higher doses, and since then, low-dose amiodarone has been recommended for treatments in several clinical settings. A meta-analysis of 4 double-blind, placebo-controlled trials involving 1,465 patients who received low-dose amiodarone (mean daily dose from 152 to 330 mg) showed a trend toward increased risk of APT with increasing dose, but this did not reach statistical significance. Another analysis of combined placebo-controlled trials involving 3,439 patients receiving a daily dose of 400 mg or less found that the rate of APT was 2.4% in the amiodarone group and 0.8% in the placebo group.

Risk management of APT is particularly important with long-term therapy. Previous reports have suggested the usefulness of a pulmonary function test based on the diffusion capacity of carbon monoxide (DL_{CO}) or assay of serum KL-6, a MUC1 mucin, for the prediction of risk and diagnosis of APT, but there has not been a cohort study to compare these markers for APT screening.

In Japan, extremely low-dose amiodarone therapy, less than 200 mg daily, has been in use since 1987. We have also used serial pulmonary functional test monitoring, including percent predicted DL_{CO} (%DL_{CO}), since 1987 and serum KL-6 monitoring since 1998, in additional to monitoring of clinical symptoms and signs, and chest X-ray to screen for APT.

The aim of this study was to evaluate the incidence and clinical risk factors of APT, and the accuracy and effectiveness of the screening tests in predicting APT in Japanese patients receiving low-dose amiodarone.

**Methods**

We reviewed the medical records of 500 consecutive Japanese patients (409 male patients (82%)), who had started amiodarone therapy at Tokyo Women’s Medical University Hospital between February 1987 and January 2002, and evaluated the results using a retrospective cohort design. We did not start amiodarone therapy in patients who had a background of obvious pulmonary fibrosis, less than 45% of %DL_{CO} or severe chronic obstructive pulmonary disease (COPD). All patients were treated with amiodarone because of ventricular or supraventricular tachyarrhythmia with structural heart disease or heart failure. The last day of follow-up was set in December 2005.
Amiodarone Therapy and Follow-up

Patients were orally loaded with amiodarone at a dose of 400 mg daily for 14 days or 800 mg daily for 7 days. In some cases, administration was begun at 200 or 300 mg daily because of concomitant organic lung disease or advanced heart failure. After the initial loading phase, amiodarone was continued at a dosage of 50–200 mg daily. The maintenance dose was adjusted while efficacy and side-effects were monitored. Most of the patients were hospitalized for at least 2 weeks while undergoing initial amiodarone loading, and received follow-up every 1–3 months at the hospital’s outpatient clinic during ongoing amiodarone therapy. Tests to monitor pulmonary function, including %DLCO and serum KL-6, were in principle performed every 3 months in the first year after the start of treatment and then every 3–6 months during amiodarone therapy. The serum KL-6 level was determined with an enzyme immunoassay kit or electrochemiluminescence immunoassay kit (Sanko Junyaku Co, Ltd, Tokyo, Japan). Plasma concentrations of amiodarone and its active metabolite, monodesethylamiodarone, were also measured by high-performance liquid chromatography.

Diagnosis of APT

The diagnosis of APT was based upon all the following criteria: (1) new onset of pulmonary symptoms such as dyspnea, cough, pleuritic chest pain, fever; (2) new chest radiographic abnormalities including on computed tomography (CT) scan; (3) recovery on discontinuation of amiodarone; and (4) no evidence supporting congestive heart failure, infectious processes or malignancy. All patients who were suspected of having APT underwent CT scan of the chest as soon as possible and the final diagnosis of APT was made from positive CT scan results. A lung biopsy was not required.

Risk Factors

One aim of this study was to identify potential risk factors for the development of APT. We assessed the following clinical and measurement factors.

Pretreatment Factors We defined factors that were already determined at the start of amiodarone therapy as pretreatment factors. We reviewed the medical history of the patients and age, sex, preexisting lung disease, %DLCO, body mass index, left ventricular ejection fraction (LVEF), New York Heart Association (NYHA) functional class, serum creatinine concentration, and serum albumin concentration at baseline were investigated as pretreatment factors.

Follow-up Factors We defined variable factors that were determined after the initiation of drug administration as follow-up factors. Age, loading dose, maintenance dose, and plasma concentrations of amiodarone and monodesethylamiodarone were considered to be follow-up factors.

Statistical Analysis

The cumulative incidence was estimated using the Kaplan-Meier method from the initiation of drug administration to the last observation day or the day of APT diagnosis. The number of patients available for the analysis, as well as the number of APT patients, was counted each year. Data on patients who discontinued amiodarone therapy only because of a marked decrease of %DLCO were censored at the time of discontinuation.

To assess the risk factors of APT, pretreatment and follow-up factors were separately entered into a multivariate analysis using Cox proportional hazard model. Because maintenance dose and blood concentration can be confounding factors, they were analyzed separately.

To evaluate the accuracy of %DLCO and serum KL-6 as screening variables, the sensitivity, specificity and likelihood ratio were calculated using 2×2 contingency tables. %DLCO was determined as positive if the last measurement value of the follow-up period had decreased 20% or more from the pretreatment value. Serum KL-6 was determined as positive if the last measurement value was 500 U/ml or more, according to the criteria for idiopathic interstitial pneumonitis. Receiver-operating characteristic (ROC) curves were made by setting various cut-off points in order to compare the characters of both screening tests. The number needed to screen (NNS) was calculated to assess the clinical efficacy of screening tests. These analyses were performed in SPSS version 11.0 (Chicago, IL, USA) and Microsoft Excel 2003 for Windows.

Each result is expressed as mean±standard deviation. A p-value of <0.05 was considered statistically significant.

Results

Clinical Characteristics

Clinical characteristics of the patients who received amiodarone therapy are summarized in Table 1. Mean age at the start of amiodarone was 53±16 years. Patients with pre-existing lung disease were 26%, including COPD, organized tuberculosis, and lung sarcoidosis. Mean LVEF was 37±18%, indicating comparatively low cardiac function. Underlying heart disease was mostly non-ischemic cardiomyopathies, including 148 dilated cardiomyopathies, 66 hypertrophic cardiomyopathies and 40 arrhythmogenic right ventricular cardiomyopathies. The indication for amiodarone was ventricular tachycardia/ventricular fibrillation in 77% of patients, and atrial fibrillation/flutter associated with heart failure or hypertrophic cardiomyopathy in the others. Implantable cardioverter defibrillator was implanted in 130 patients. Average loading dose of amiodarone was 385±164 mg daily and the maintenance dose was 141±70 mg.

<table>
<thead>
<tr>
<th>No. of patients</th>
<th>500</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>53±16</td>
</tr>
<tr>
<td>M/F</td>
<td>409/91</td>
</tr>
<tr>
<td>Underlying heart disease</td>
<td></td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>142 (28%)</td>
</tr>
<tr>
<td>Nonischemic cardiomyopathies</td>
<td>275 (55%)</td>
</tr>
<tr>
<td>Valve disease</td>
<td>27 (5%)</td>
</tr>
<tr>
<td>Others</td>
<td>56 (11%)</td>
</tr>
<tr>
<td>LVEF</td>
<td>38±18</td>
</tr>
<tr>
<td>NYHA functional class</td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>181 (36%)</td>
</tr>
<tr>
<td>II</td>
<td>182 (36%)</td>
</tr>
<tr>
<td>III</td>
<td>58 (12%)</td>
</tr>
<tr>
<td>IV</td>
<td>79 (16%)</td>
</tr>
<tr>
<td>Concomitant lung disease</td>
<td>26 (5%)</td>
</tr>
<tr>
<td>Amiodarone</td>
<td></td>
</tr>
<tr>
<td>Loading (mg daily)</td>
<td>385±164</td>
</tr>
<tr>
<td>Maintenance (mg daily)</td>
<td>141±70</td>
</tr>
<tr>
<td>Duration of therapy (months)</td>
<td>48±43</td>
</tr>
</tbody>
</table>

Data are mean±SD or number (%). NYHA, New York Heart Association; LVEF, left ventricular ejection fraction.
daily. These doses were considered to be relatively low compared with previous reports. Total follow-up period was 2003 person-years, and mean follow-up period was 48±43 months.

**Incidence and Prognosis of APT**

Of the 500 patients, 40 were diagnosed with APT (8.0%). In practice, a decrease in %DLCO or an increase in serum KL-6 level alone did not prompt discontinuation of amiodarone, but such patients were checked for APT. Another 22 patients, not clinically APT, were discontinued because they were judged to be high risk based on a marked decrease of %DLCO. No patient was discontinued only because of an increased KL-6 level.

Follow-up period and cumulative APT incidence are shown in Fig 1. Cumulative incidence was 4.2%, 7.8%, and 10.6% at 1, 3, and 5 years, respectively, after the start of amiodarone. The annual cumulative rate was estimated to be 2.1%. The lower table shows the numbers of APT patients and patients available for the analysis each year.

Among the 40 patients who developed APT, 23 improved with discontinuation of amiodarone only, but 17 required corticosteroid therapy. Intravenous high-dose of corticosteroid was given to 4 patients, but 2 patients died from respiratory failure. The mortality rate was 5% (2 of 40 APT patients).

**Risk Factors of APT**

The pretreatment risk assessment of APT is shown in Table 2. In the multivariate analysis, age at the start of...
Amiodarone therapy was a highly predictive risk factor of APT. Complicating lung disease or pretreatment %DLCO was not a significant factor in this study. NYHA functional class or LVEF was not a predictive factor of APT.

The risk assessment of the follow-up factors is summarized in Table 3. Age, maintenance dose of amiodarone and plasma monodesethylamiodarone concentration were independent predictive factors of APT. The respective hazard ratio (HR) of maintenance dose and plasma monodesethylamiodarone concentration was 1.88 per 50mg increase.
APT Screening Test Using %DLco or Serum KL-6

Diagnostic values of %DLco and serum KL-6 level are shown in Table 4. For %DLco, individual decreases of 10%, 15%, and 20% were analyzed as a predictor of APT. Of these, high sensitivity of 76% (95% confidence interval (CI) 62–91) was obtained with a ≥20% decrease and high specificity of 74% (95% CI 69–78) was obtained with a ≥20% decrease. Whereas for KL-6, the sensitivity was 25% (95% CI 8–42) and specificity was 91% (95% CI 88–95). Sensitivity was higher for %DLco than for KL-6.

ROC curves for the screening tests are shown in Fig 3. The true-positive ratio (sensitivity) and false-positive ratio (1-specificity) were plotted for various cut-off values of each test. ROC analysis demonstrated that the predictive value of follow-up %DLco tended to be superior to that of follow-up serum KL-6. Using the estimated incidence per year (2.1%) and the sensitivity value of 10% decrease in %DLco (76%), the NNS for %DLco every 3 months and every 6 months with a cut-off point of 15% decrease were 279 and 140, respectively. The median leading time of %DLco with a cut-off point of 15% decrease was 583 days.

Discussion

This study is retrospective in nature, but can be considered as a cohort design because it is based on patients treated at Tokyo Women's Medical University. APT is a serious, potentially fatal, side-effect of amiodarone, but the etiology and mechanism of development of APT remain unclear.

In the 1980s, the use of high doses of amiodarone was identified as a major cause of APT. The first large study in 1990, reported by Dusman et al., showed that the prevalence rate reached 9.1% at 60 months of therapy and was 5.8% in total in patients receiving a daily dose of 400–500 mg. It is generally believed that low-dose therapy is safer. Sunderji et al. reported an incidence of APT of 1.6% in patients with a daily dose of 400 mg or less, considerably lower than the previously reported incidence of 5–10% in patients with daily doses of greater than 400 mg. The results from the Congestive Heart Failure-Survival Trial of Antiarrhythmic Therapy (CHF-STAT) showed that the 1.1% incidence of APT in patients receiving a daily dose of 300 mg was not significantly higher than the 0.8% incidence in patients receiving placebo. Moreover, a meta-analysis of relative low-dose (<400 mg daily), placebo-controlled trials showed a 1.9% incidence of APT in 738 patients receiving amiodarone, but a 0.7% incidence in 727 patients receiving placebo; the combined odds ratio was 2.2, indicating a trend toward an increase in the risk of APT.

In the 1990s, the recommended maintenance dose of amiodarone was reduced to 200 mg daily to avoid adverse effects. However, a recent report in patients receiving low-dose amiodarone concluded that APT could occur at a daily dose of 200 mg. In the present study, APT occurred at extremely low maintenance doses, less than 200 mg daily, of amiodarone. APT incidence was estimated to be 2.1% per year, which is not low compared with the 1.8% per year in a meta-analysis of 6,500 patients involved in placebo-controlled amiodarone trials. A retrospective multicenter registered study in Japan, the Nippon ICD Plus Pharmacologic Option Necessity (NIPPON)-pre study, in ICD treated patients with organic heart disease and ventricular tachyarrhythmia showed 11 patients (3.1%) developed APT among 247 with concomitant amiodarone during mean follow-up period of 37 months after ICD implantation. That is a result from patients who only used amiodarone as an adjunctive therapy to ICD, but the present study included several patients who started amiodarone therapy for the prevention of sudden cardiac death in the non-ICD era, or who started amiodarone in an emergency setting. Other studies in small numbers of Japanese patients with atrial tachyarrhythmia showed that 2.7–3.6% of patients receiving amiodarone developed APT during mean follow-up periods of 30–36 months. Although the backgrounds, number of subjects, or follow-up periods were different, there is a relatively high incidence of APT in Japanese patients. The reason why it should be higher than in previous reports from Europe and the United States, despite the extremely low dose of amiodarone used in Japanese patients, is unclear. However, ethnic differences in drug side-effects seem to exist. An interesting report from Hong Kong has shown that 12 patients (1.9%) developed APT among 613 Chinese patients receiving 200 mg daily during a mean follow-up period of 14 months. Recently, gefitinib, leflunomide, and bortezomib were found to induce a markedly higher incidence of pulmonary toxicity in Japanese patients than in patients in Europe and the United States. For the epidermal growth factor receptor (EGFR) inhibitor gefitinib, Japanese or East Asian ethnicity is considered to be one of the clinical predictive factors for response, and being positive for EGFR mutation in exons 18–24 in cancer cells has a strong correlation with response, especially in the Asian population. Japanese or East Asian ethnicity may also be associated with gefitinib-induced pulmonary toxicity. Although the molecular mechanism of this pulmonary toxicity is unknown, the findings indicate that genetic factors may play a role in sensitivity to gefitinib. Japanese ethnicity may also be a contributing factor in APT. Further investigation is needed to evaluate the association between genetic factors and APT.

Two possible mechanisms of APT have been suggested: (1) a direct toxic effect and (2) an immune-mediated hypersensitivity-based mechanism. The common histological findings of APT are alveolar damage and foamy intra-alveolar macrophages. Lung cell injury has been suggested to be mediated by changes in proteins, lipids and several lysosomal enzymes regulation of apoptosis etc. It was recently suggested that metabolites containing the diethylenoethoxy group, such as monodesethylamiodarone, have a crucial role in toxicity for alveolar macrophages. Amiodarone and monodesethylamiodarone accumulate in peripheral tissues to very high levels over long periods because of their peculiar pharmacokinetics, large distribution volume and long elimination half-life. Pollak et al. found that the monodesethylamiodarone/amiodarone ratio increased in the first few months of therapy and stabilized at approximately 0.85 by the end of the first year, and that APT patients showed abnormally high ratios. Increased duration of therapy tends to increase the prevalence rate of APT and the risk of developing APT. It is possible that prolonged drug accumulation, especially of monodesethylamiodarone, could be associated with lung injury via a direct toxic effect. As for the prevalence rate per year, in the present
study the first-year value of 4.2% was higher than the following years' values of 2.1%, which seems consistent with a previous follow-up study. The etiology of APT occurring in the first year may not necessarily be the same as that developing in the late phase, though the mechanisms are not well understood. The relatively high incidence of APT in the first year might be associated, at least in part, with a hypersensitivity mechanism, including allergic reaction, rather than direct toxic action.

In our study, the only pretreatment risk factor for the development of APT was age, according to multivariate analysis. Advanced age is well known to be an independent risk factor. Previous studies have suggested that pre-existing lung disease, especially COPD, might predispose the patient to APT.5,6 However, other prospective studies failed to show that pre-existing lung disease or a pretreatment %DLCO abnormality was related to development of APT.7,8,9 Our results also showed that complicating lung disease or pretreatment %DLCO was not a significant factor, but we did not start amiodarone in patients who had a background of obvious pulmonary fibrosis, less than 45% of %DLCO or severe COPD. Thus, our result does not show that amiodarone therapy is safe in patients with lung diseases. Our findings indicate that the incidence of APT increases with higher age, higher maintenance dose and higher plasma monodeuteriumiodamide concentration, in agreement with previous reports, even though a low-dose regimen was used in the patients. Further decreasing the maintenance dose of amiodarone in Japanese patients might be appropriate, and should be investigated in a future study.

Margo et al prospectively evaluated 89 patients receiving amiodarone during a mean follow-up period of 20 months, and reported that an individual decrease in %DLCO of 15% or 20% gave a sensitivity of 100% and 88%, and a specificity of 89% and 94%, respectively, for the diagnosis of APT.10,11 Gleadhill et al also evaluated 91 patients receiving amiodarone during a mean follow-up period of 12 months, and reported that an individual decrease in %DLCO of 20% gave a sensitivity of 100% and a specificity of 83% for the diagnosis of APT.30 In our study, the sensitivity and specificity of 15% or 20% decrease in %DLCO were lower than those in the previous reports.30 This may in part be related to frequently monitoring %DLCO during the longer follow-up period in our study, because of the large inherent variability in this test. In our study, however, values of the NNS for an individual decrease in %DLCO every 3 and 6 months seem not to be high from the viewpoints of prevention and early detection of APT, because these values are lower than those for mammography in women aged 50–59.12

KL-6 is a high-molecular-weight, mucin-like glycoprotein secreted by proliferating type II alveolar pneumocytes, and is a sensitive marker of disease activity in various interstitial lung diseases.33 An increase in the level of circulating KL-6 has been described in APT patients;13 but its sensitivity and specificity as a predictor of APT are unclear. In our study, the utility of monitoring serum KL-6 levels as a predictor of APT occurrence was not confirmed, and a cutoff point of KL-6 of 500 U/ml was also inappropriate as a potential predicting value. A recent report showed that the overall sensitivity of serum KL-6 in detecting drug-induced pneumonia was 53.3%, which is lower than its sensitivity in detecting other interstitial lung disease.28 However, increased serum KL-6 has been reported to be useful for detecting the presence of interstitial pneumonias and drug-induced pneumonia with diffuse alveolar damage or a chronic interstitial pneumonia pattern on high-resolution CT.23 Our results showed that the specificity of serum KL-6 was higher than that of %DLCO, so we consider that serum KL-6 is useful for assessing a background of interstitial lung disease before amiodarone therapy, the status of APT after its occurrence and the efficacy of the treatment for APT.

Conclusion
APT occurred in Japanese patients even on extremely low-dose amiodarone, and the incidence increased with increasing duration of therapy. Higher age, higher maintenance dose and higher plasma monodeuteriumiodamide concentration were risk factors. Because there is no safe dose of amiodarone therapy, we should consider whether a further decrease of the maintenance dose would reduce the incidence of pulmonary toxicity, at least in Japanese patients. Our results also re-emphasize the importance of suitable screening tests for efficacy and side-effects.

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References


