Clinical Features of Amiodarone-Induced Pulmonary Toxicity

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The incidence and clinical predictors of amiodarone pulmonary toxicity were examined in 573 patients treated with amiodarone for recurrent ventricular (456 patients) or supraventricular (117 patients) tachyarrhythmias. Amiodarone pulmonary toxicity was diagnosed in 33 of the 573 patients (5.8%), based on symptoms and new chest radiographic abnormalities (32 of 33 patients) and supported by abnormal pulmonary biopsy (13 of 14 patients), low pulmonary diffusion capacity (DLCO) (nine of 13 patients), and/or abnormal gallium lung scan (11 of 16 patients). Toxicity occurred between 6 days and 60 months of treatment for a cumulative risk of 9.1%, with the highest incidence occurring during the first 12 months (18 of 33 patients). Older patients developed it more frequently (62.7±1.7 versus 57.4±0.5 years, p=0.018), with no cases diagnosed in patients who started therapy at less than 40 years of age. Gender, underlying heart disease, arrhythmia, and pretreatment chest radiographic, spirometric, or lung volume abnormalities did not predict development of amiodarone pulmonary toxicity, whereas pretreatment DLCO was lower in the group developing it (76.0±5.5% versus 90.4±1.4%, p=0.01). There was a higher mean daily amiodarone maintenance dose in the pulmonary toxicity group (517±25 versus 409±6 mg, p<0.001) but no difference in loading dose. No patient receiving a mean daily maintenance dose less than 305 mg developed pulmonary toxicity. Patients who developed toxicity had higher plasma desethylamiodarone (2.34±0.18 versus 1.92±0.04 μg/ml, p=0.009) but not amiodarone concentrations during maintenance therapy. Death due to pulmonary toxicity occurred in three of 33 patients (9.1%). In conclusion: 1) amiodarone pulmonary toxicity occurred in 5.8% of patients and was more common with a higher amiodarone maintenance dose, advanced age, lower pretreatment DLCO, and higher plasma desethylamiodarone concentrations; and 2) pretreatment chest radiographic, spirometric, and lung volume abnormalities were not predictive for development of amiodarone pulmonary toxicity. (Circulation 1990;82:51–59)

Amiodarone hydrochloride, although generally effective as an antiarrhythmic drug,1–3 has both complex pharmacokinetic properties and the potential for a wide range of adverse effects.4 Perhaps the most serious side effect of amiodarone has been pulmonary toxicity. Initially reported in 1980,5 amiodarone-associated pulmonary toxicity has been reported to occur in 1–17% of treated cases and to have a potentially fatal course.1,6–13 Risk factors, such as underlying pulmonary disease, have been suggested in some8,12,13 but not all9 reports.

The present study was undertaken to determine the incidence and clinical features associated with amiodarone-induced pulmonary toxicity in a large series of patients treated at a single medical center. Also examined were the relations of preexisting pulmonary abnormalities, drug doses, and plasma drug concentrations to the development of amiodarone pulmonary toxicity.

Methods

Patients

The study population comprised 573 patients who were treated at the Indiana University Medical Center and initiated amiodarone therapy between April
TABLE 1. Clinical Characteristics of Patients Treated With Amiodarone

<table>
<thead>
<tr>
<th>Patients (n)</th>
<th>573</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yrs)</td>
<td>mean±SD 57.7±12.6, range 5–88</td>
</tr>
<tr>
<td>Sex (male/female)</td>
<td>451/122</td>
</tr>
<tr>
<td>Pretreatment arrhythmia</td>
<td>VT or VF 456, SVT 117</td>
</tr>
<tr>
<td>Underlying heart disease</td>
<td>ischemic 346, cardiomyopathy 94, valvular 47, primary electrical 62, Wolff-Parkinson-White 14, congenital 9, fibroelastosis 1</td>
</tr>
</tbody>
</table>

VT, nonsustained or sustained ventricular tachycardia; VF, ventricular fibrillation; SVT, supraventricular tachycardia.

1977 and March 1986. All patients receiving amiodarone for more than 3 days during this time span were included. The clinical characteristics of these patients are outlined in Table 1.

Amiodarone Administration Protocol

Amiodarone therapy was administered in loading and maintenance dose phases. Initially in our experience with amiodarone, the loading phase was 800 mg/day administered for up to 6–8 weeks. Based on clinical and pharmacokinetic data,14 this loading dose was later modified to 1,600 mg/day for 1 week, followed by 800 mg daily for 1 month. During maintenance therapy, daily amiodarone doses ranged from 50 to 800 mg/day, determined by control of the clinical arrhythmia and the occurrence of drug-related side effects. Plasma concentrations of amiodarone and its metabolite, desethylamiodarone, were measured by high performance liquid chromatography15 every 6–12 months during follow-up.

Pulmonary Follow-up Protocol

A pulmonary follow-up protocol was established in 1980, once the potential for pulmonary toxicity was identified. Chest radiographs and, when feasible, measurements of spirometry, lung volume, and diffusion capacity were obtained pretreatment. These pulmonary function measurements included 1) second forced expiratory volume (FEV₁), forced vital capacity (FVC), mid–forced expiratory flow (FEF₂₅–₇₅), the ratio of FEV₁ to FVC (FEV₁/FVC), total lung capacity (TLC) as measured by nitrogen washout methods, and diffusion capacity (DLCO) as measured by single breath carbon monoxide dilution. All data were recorded as absolute values and calculated percent predicted using conventional corrections for body surface area, age, and sex of the patient.16 From April 1977 through March 1986, all patients initiated therapy at our institution and were seen in follow-up every 3 months for the first 2 years of drug therapy and every 6 months thereafter in the Investigational Drug Clinic by a cardiologist experienced with amiodarone therapy. Chest radiographs were repeated at 3–6-month intervals in more than one half of the patients during the follow-up period, or sooner if symptoms dictated. Pulmonary function tests were repeated if new symptoms or chest radiographic abnormalities suggested pulmonary toxicity.

After the release of amiodarone for noninvestigational use in March 1986, some patients opted for continued follow-up with their own referral physician. These patients, their physicians, or both were contacted by phone to ascertain pertinent follow-up information.

Other Investigations

Additional testing was performed to establish or confirm the diagnosis of amiodarone pulmonary toxicity in most cases. Gallium-67 citrate, 2–5 mCl, was administered intravenously, and scintigraphic images were obtained 48 hours after injection of the radiisotope. Increased lung uptake was interpreted as consistent with an inflammatory process.17 Light and electron microscopic examination of lung tissue obtained by bronchoscopic or open lung biopsy was conducted for the following pathologic changes6,13: 1) hyperplasia of type II pneumocytes, 2) alveolar septal thickening, 3) intra-alveolar accumulation of foamy macrophages and pneumocytes, and 4) fibrosis. Bronchoalveolar lavage, more recently described in patients with suspected amiodarone lung toxicity,18,19 was done inconsistently in the present study. In all cases, alternative etiologies such as congestive heart failure, infection, or malignancy were excluded by right heart catheterization, trials of diuretic therapy, sputum examination, or more detailed radiographic procedures. Amiodarone therapy was discontinued when the diagnosis of toxicity was made.

Diagnostic Criteria

Amiodarone-induced pulmonary toxicity was a clinical diagnosis that required two or more of the following criteria: 1) new onset of pulmonary symptoms such as dyspnea, cough, or pleuritic chest pain; 2) new chest radiographic abnormality such as an interstitial or alveolar infiltrate; 3) a decrease in the DLCO of 20% from the pretreatment value, or if none was available, a value less than 80% of predicted; 4) abnormal lung uptake with gallium-67 radioisotope; and 5) characteristic histologic changes of lung tissue obtained by bronchoscopic or open lung biopsy.6,13 Exclusion of alternative etiologies such as congestive heart failure, infection, or malignancy was done in all patients.

Statistics

Comparison between patients with and without amiodarone pulmonary toxicity were made using a t test for continuous variables. Discrete variables were analyzed by a χ² test. Fisher's exact test was used for 2×2 tables. Cumulative survival without pulmonary...
toxicity was calculated by the Kaplan-Meier method. A p value of less than 0.05 was considered significant. The duration of the therapy was computed as the length of time from the start of amiodarone therapy until either the end of the study follow-up, death, discontinuation of therapy, loss of follow-up (last date for which reliable information was available), or the development of pulmonary toxicity. A survival curve for survival without pulmonary toxicity was calculated using the Kaplan-Meier product moment technique. Failure was development of pulmonary toxicity. All other endpoints as described above were considered censored data. Figure 1 is the inverse of the survival curve or the cumulative incidence of amiodarone-associated pulmonary toxicity.

**Results**

**Incidence and Time Course for Toxicity**

Of the 573 patients who received amiodarone, 33 developed pulmonary toxicity, resulting in an overall incidence of 5.8%. The cumulative incidence of amiodarone pulmonary toxicity was 9.1% at 121 months of therapy using survival analysis (Figure 1). The highest risk for the development of toxicity, corresponding to the steepest portion of the curve, occurred during the first 12 months of therapy. After 12 months, the cumulative incidence of toxicity continued to rise steadily, reaching 9.1% at 60 months of therapy. No cases of amiodarone-induced pulmonary toxicity developed after 60 months of therapy. The longest treated patient was followed for 121 months. The shortest dosing interval in which pulmonary toxicity occurred was 6 days; this patient had amiodarone discontinued 6 days after beginning therapy (800 mg/day) because of recurrent arrhythmia. Upon preoperative evaluation 1 month later for left ventricular aneurysmectomy and endocardial resection, he was found to have interstitial infiltrates on chest radiograph, mild dyspnea, and abnormal gallium lung uptake; histologic examination of lung tissue obtained by bronchoscopy and confirmed by open lung biopsy was consistent with pulmonary toxicity.

Before the institution of a specific pulmonary follow-up protocol (1977–80), 20 patients discontinued amiodarone therapy. None of these patients had symptoms or signs suggestive of pulmonary toxicity, and only one patient discontinued the drug for unknown reasons.

Three hundred forty-one of the 573 patients were followed at Indiana University. Ninety-three percent of these subjects had had chest radiographs within 6 months of the conclusion of the study. We have no data among the 232 patients followed outside of Indiana University regarding completeness of chest radiography follow-up, after they were no longer followed by us, beginning March 1986.

**Presenting Symptoms**

The presenting symptoms of amiodarone-induced pulmonary toxicity were known in 28 patients. The majority (71%) had dyspnea as the initial symptom. Other symptoms were cough (25%), fever (21%), nausea (7%), weakness or fatigue (7%), weight loss (4%), and pleuritic chest pain (4%).

**Diagnostic Tests**

The diagnostic tests used to establish and confirm the diagnosis of amiodarone pulmonary toxicity are outlined in Table 2. The diagnosis of pulmonary toxicity was made solely on the basis of presenting symptoms and chest radiographic abnormalities in six of 33 patients. In 25 patients, additional abnormalities in either DLCO, gallium scan, histology, or a

**Table 2. Diagnostic Tests Performed in Patients With Amiodarone Pulmonary Toxicity**

<table>
<thead>
<tr>
<th>Test</th>
<th>n</th>
<th>Normal</th>
<th>Abnormal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chest radiograph</td>
<td>33</td>
<td>1</td>
<td>32</td>
</tr>
<tr>
<td>DLCO</td>
<td>13</td>
<td>4</td>
<td>9</td>
</tr>
<tr>
<td>Gallium scan</td>
<td>16</td>
<td>5</td>
<td>11</td>
</tr>
<tr>
<td>Histology</td>
<td>14</td>
<td>1*</td>
<td>13</td>
</tr>
</tbody>
</table>

DLCO, diffusion capacity of lung using single breath carbon monoxide test.

*Inadequate specimen.
combination of these were present to confirm the diagnosis, whereas two patients had pulmonary toxicity diagnosed only at postmortem examination. New chest radiographic abnormalities occurred in 32 of the 33 patients and were most often diffuse interstitial pulmonary infiltrates, occasionally alveolar in distribution, and often involved the upper lobes. Two patients had pleural effusions. The patient without a radiographic pulmonary abnormality presented with increased exertional dyspnea after 12 months of amiodarone treatment. A 42% decline in DLCO and diffuse gallium lung uptake suggested the diagnosis of pulmonary toxicity. DLCO determinations were available in 13 patients who presented with toxicity and were abnormally low in nine. Restrictive lung function (decreased FVC and TLC and increased FEV1/FVC) occurred in all 15 patients who had these parameters measured.

Gallium lung scans revealed abnormal radioisotope uptake in 11 of 16 patients and generally correlated with the abnormalities noted on chest radiograph. Of the five patients with normal gallium scans, two were imaged 2–4 weeks after amiodarone was discontinued, one had histologic evidence for pulmonary fibrosis at postmortem examination without the presence of inflammatory cells, and one had the gallium scan done 2 days after amiodarone discontinuation, with biopsy confirming toxicity. The remaining patient had superimposed congestive heart failure, the degree of which was not thought severe enough to solely account for the clinical picture, although lung biopsy was not performed.

Fourteen patients had histologic examination of lung tissue, which was obtained by open lung biopsy in three patients, transbronchial biopsy in seven patients, and combined open lung and transbronchial biopsy in one patient. Three patients had histologic examination postmortem. Thirteen biopsies were abnormal by the criteria outlined previously. One patient had an inadequate specimen obtained by transbronchial biopsy.

Associated Clinical Characteristics

Clinical and demographic characteristics were examined for possible association with the occurrence of amiodarone pulmonary toxicity. Patients with and without amiodarone pulmonary toxicity were not different in gender, underlying heart disease, presenting arrhythmia, or concomitant antiarrhythmic medications. Patients who developed amiodarone pulmonary toxicity were older at initiation of therapy (62.7±1.7 years) compared with those without pulmonary toxicity (57.4±0.5 years, p=0.018). No cases of pulmonary toxicity were diagnosed in patients who started therapy less than or equal to 40 years of age (N=57), whereas the incidence of toxicity was fairly uniform for each decade of life in patients beyond 50 years of age (Figure 2).

### Pretreatment and Follow-up Radiographs

Analysis of pretreatment chest radiographs revealed no significant difference between patients who did and did not develop pulmonary toxicity. During follow-up, new chest radiographic abnormalities developed in 98 of 571 patients (17%). These new abnormalities were attributed to amiodarone pulmonary toxicity in 32 patients, whereas the remainder were secondary to congestive heart failure (34 patients), atelectasis (seven patients), chronic obstructive pulmonary disease (six patients), malignancy (four patients), and infection (three patients). Twelve remaining patients had chest radiographic abnormalities of unknown etiology that resolved spontaneously despite continuation of amiodarone.

### Pretreatment Pulmonary Function Tests

Pretreatment pulmonary function tests of the groups with and without pulmonary toxicity were compared. There was no significant difference in measured lung volumes or spirometry between these two groups (Table 3). Figure 3 compares the pretreatment pulmonary function tests of the two groups.

**Table 3.** Pretreatment Spirometric and Lung Volume Measurements in Patients Treated With Amiodarone

<table>
<thead>
<tr>
<th>Test</th>
<th>APT−</th>
<th>APT+</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>FVC (l)</td>
<td>3.42±0.04</td>
<td>3.42±0.23</td>
<td>0.99</td>
</tr>
<tr>
<td>(389)</td>
<td>(26)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>FEV1/FVC (%)</td>
<td>76.1±0.5</td>
<td>73.1±0.18</td>
<td>0.15</td>
</tr>
<tr>
<td>(389)</td>
<td>(26)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>FEF25–75 (l/sec)</td>
<td>2.19±0.06</td>
<td>1.77±0.25</td>
<td>0.10</td>
</tr>
<tr>
<td>(389)</td>
<td>(26)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TLC (l)</td>
<td>5.71±0.10</td>
<td>5.34±0.32</td>
<td>0.25</td>
</tr>
<tr>
<td>(316)</td>
<td>(16)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Values are mean±SEM; the number in parentheses denotes the number of patients available for analysis.

APT−, amiodarone pulmonary toxicity absent; APT+, amiodarone pulmonary toxicity present; FVC, forced vital capacity; FEV1/FVC, ratio of 1-second forced expiratory volume to forced vital capacity; FEF25–75, mid–forced expiratory flow; TLC, total lung capacity.
Amiodarone-Induced Pulmonary Toxicity

Comparison of pretreatment diffusion capacity (DLCO) and percent of predicted DLCO between the groups with amiodarone pulmonary toxicity (APT +; stripped bars) and without (APT -; unfilled bars). Numbers within each bar represent number of patients available for analysis.

Amiodarone Drug Dose Analysis

Amiodarone dose data were calculated by two methods. The initial analysis defined the loading period as the number of days amiodarone was administered before a decrease to a stable dose. There was no significant difference between the group with and the group without amiodarone pulmonary toxicity with respect to the actual length of the loading period (mean, 35 ± 12; range, 6–56 days versus mean, 36 ± 16; range, 3–83 days, p = 0.47) and the mean daily loading dose (838 ± 40 versus 848 ± 11 mg, p = 0.79). During the maintenance period, however, the patients who developed toxicity received a significantly higher mean daily dose of amiodarone when compared with the group without toxicity (515 ± 25 versus 409 ± 6 mg, p < 0.001).

The second analysis standardized the loading phase of amiodarone administration to be the first 30 days of drug treatment. During the loading period, there was no significant difference between the group with and the group without development of amiodarone pulmonary toxicity in the mean daily amiodarone dose (816 ± 35 versus 832 ± 10 mg, p = 0.70). During the

Although a normal pretreatment value had a negative predictive value of 97%.

Plasma Drug Concentrations

Plasma concentrations of amiodarone and its metabolite, desethylamiodarone, were measured during the maintenance period of amiodarone therapy (Figure 5). There was no difference in mean plasma amiodarone concentration between the groups with and without toxicity (3.04 ± 0.38 versus 2.83 ± 0.06 μg/ml, p = 0.46). However, the mean plasma desethylamiodarone concentrations were significantly higher in the group with pulmonary toxicity compared with the group without toxicity (2.34 ± 0.18 versus 1.92 ± 0.04 μg/ml, p = 0.009). There was a mean of 3.2 (range, 1–9) determinations of plasma drug and metabolite concentrations done per patient in the group with amiodarone pulmonary toxicity and a mean of 3.9 (range, 1–12) in the group without.

Figure 3. Comparison of pretreatment diffusion capacity (DLCO) and percent of predicted DLCO between the groups with amiodarone pulmonary toxicity (APT +; stripped bars) and without (APT -; unfilled bars). Numbers within each bar represent number of patients available for analysis.

Figure 4. Frequency distribution of pretreatment percent of predicted diffusion capacity (DLCO) and development of amiodarone pulmonary toxicity (APT +; stripped bars) versus no toxicity (APT -; unfilled bars). Numbers in each bar represent number of patients in each group.
maintenance period, however, the patients who developed toxicity received a significantly higher mean daily dose of amiodarone when compared with the group without toxicity (517±25 versus 409±6 mg, p<0.001) (Figure 6). No patient who received an average daily amiodarone dose of less than 305 mg during maintenance therapy developed pulmonary toxicity. There was no relation between age and maintenance dose; younger patients did not receive a lower drug dose.

The two initial loading dose strategies (1,600 versus 800 mg) were also analyzed for a possible association with the development of amiodarone pulmonary toxicity. The proportion of patients starting drug treatment with either dose was the same for both groups with and without toxicity (p=0.97).

Follow-up of Patients with Pulmonary Toxicity

Three of the 33 patients with toxicity (9.1%) died as a direct result of this complication. The time course from diagnosis to death ranged from 4 to 30 days. Eight additional patients with amiodarone pulmonary toxicity died during follow-up; five deaths were attributed to congestive heart failure and one death each to sudden cardiac arrest, alcoholic liver disease, and metastatic breast cancer. Ten patients were treated with glucocorticoids, of whom one died of pulmonary toxicity. Two deaths occurred in the remaining 23 patients not treated with steroids. Two patients diagnosed with amiodarone pulmonary toxicity had a subsequent rechallenge with the drug. One patient developed progressive pulmonary infiltrates associated with diffuse gallium uptake in the lungs, whereas the second patient did not develop symptoms or signs suggestive of pulmonary toxicity despite similar drug dosages for both trials.

There were 197 total deaths in this patient population during the follow-up period, of which three were attributed to pulmonary toxicity as outlined above. One hundred forty-nine were due to a cardiac etiology, and 24 were noncardiovascular in origin. Twenty-one patients had unknown causes of death although symptoms suggesting pulmonary toxicity were not reported antemortem.

Discussion

In this large series of patients treated with amiodarone, 33 of 573 patients presented with overt clinical evidence of pulmonary toxicity. These patients usually were symptomatic, had new radiographic abnormalities, and had additional diagnostic studies to help confirm the diagnosis. The diagnosis was made by considering a constellation of clinical and laboratory findings, as no single test is pathognomonic for the disorder.

Incidence and Diagnosis of Toxicity

The reported incidence of amiodarone pulmonary toxicity in the literature depends on the diagnostic criteria used. Our incidence of 5.8% is similar to that previously reported \(^6, \^8, \^13\) and was based on the appearance of new symptomatology, most frequently dyspnea and cough, and confirmed with additional diagnostic testing, including radiographic and nuclear imaging, pulmonary function testing, and histologic examination. Pulmonary toxicity from amiodarone shares features with other drug-induced pneumonitis, \(^19, \^20\) including the presence of activated inflammatory cells in the lungs that may be detected by the accumulation of gallium. \(^17, \^21\) Microscopic pathologic changes noted with lung biopsy likewise
resembled other toxic drug effects in the lung and were not pathognomonic for amiodarone toxicity, but their presence was helpful in supporting the diagnosis. Smith et al and Haffajee et al have both reported a low incidence (1%) of pulmonary toxicity although the diagnosis in these studies relied mostly on radiographic abnormalities without histologic support. This difference in diagnostic criteria and also relatively short follow-up (mean, 24 and 9 months, respectively) may be responsible in part for the low incidence of amiodarone pulmonary toxicity in these studies. A higher incidence (17%) of toxicity was reported by Magro et al, who used similar clinical diagnostic criteria to those used in the present study but emphasized symptoms and radiographic abnormalities without the aid of DLCO abnormalities. Differences in the patient populations studied and criteria used to make the diagnosis of amiodarone pulmonary toxicity may account for the observed discrepancies between our findings and those of Magro et al. Bronchoalveolar lavage, although not applied systematically in the present study, has been used to describe the cytologic changes that occur during amiodarone therapy, but its role in drug-induced toxicity remains to be defined.

Demographic Factors Predisposing to Toxicity

When demographic parameters were analyzed, a higher occurrence of pneumonitis was found in the older patients. There were no cases of amiodarone pulmonary toxicity in those patients who started therapy at an age less than 40 years. This latter finding most likely explains the significant age difference found between our two groups with and without toxicity. Other clinical characteristics such as gender, underlying heart disease, and presenting arrhythmia were not identified as risk factors for development of toxicity. The highest risk for developing toxicity occurred during the first 12 months of treatment, and no new cases were diagnosed after 60 months of therapy. This peak in incidence early in treatment has also been observed by others.

Radiographic Abnormalities

Pretreatment chest radiographic abnormalities did not identify a subset of patients at risk for developing pulmonary toxicity. New radiographic abnormalities were observed in 98 patients, but on further investigation, 67% of these were attributable to etiologies other than amiodarone toxicity. We currently recommend surveillance chest radiographs at 3–6-month intervals during maintenance amiodarone therapy, especially during the first 12 months when the risk appears to be highest. The use of routine chest radiographs during maintenance therapy complements the occurrence of new symptomatology, as the latter can be subtle and nonspecific, especially in patients with coexisting congestive heart failure or chronic obstructive lung disease.

A weakness of this analysis is our uncertainty regarding the extent to which chest radiography follow-up was obtained in patients not followed directly by us after March 1986. Though we believe that chest radiographic films were obtained at least every 6 months in most of those 232 patients, if they were not, then some cases of pulmonary toxicity could have been missed.

Pulmonary Function Testing Including Diffusion Capacity

Pretreatment spirometric or lung volume measurements were not helpful in identifying a high-risk group for developing pulmonary toxicity. An abnormally low pretreatment percent of predicted DLCO (i.e., less than 80%) did allow identification of patients who were at increased risk for developing toxicity. The wide range of DLCO values in both groups, with and without toxicity, did not allow for a specific discriminating pretreatment value that was predictive for the subsequent development of toxicity. When the data were analyzed using less than 80% of the predicted DLCO as the criterion for pretreatment abnormality, the sensitivity and specificity were only 65% and 68%, respectively, and the positive predictive value 11%. The negative predictive value of a normal pretreatment percent of predicted DLCO was 97%, however, and identified a group of patients at low risk for developing pulmonary toxicity. With the onset of pulmonary toxicity, a restrictive physiologic pattern was seen with a decrease in FVC and TLC and an increase in the FEV1/FVC ratio.

The identification of a high-risk subgroup based on an abnormally low pretreatment DLCO is consistent with the findings of Kudenchuk et al, who found a relative risk of 9.8 for development of pulmonary toxicity in patients with an abnormal baseline chest radiograph film and DLCO of less than 80% of predicted. This contrasts with Magro et al, who found that the DLCO singly or in combination with radiographic abnormalities did not predict development of pulmonary toxicity in their patients.

Based on our present data, it would appear that amiodarone should not be withheld solely on the basis of pre-existing lung disease as judged by either radiographic or pulmonary function criteria. With mediocre sensitivity and specificity and poor positive predictive value, pretreatment DLCO abnormalities should not singly negate amiodarone therapy but rather should identify patients who should be followed closely for developing toxicity. As already emphasized by Horowitz, the effect of pulmonary toxicity can be devastating, and patients with pre-existing lung disease and decreased reserve tolerate its development poorly.

Amiodarone Dose and Relation to Toxicity

The development of toxicity may be related to amiodarone dose, as there was a higher average daily dose administered to those patients who subsequently developed toxicity during the maintenance therapy. This relation of dose to the development of toxicity has been found by others. Our change to
higher initial loading doses (1,600 mg/day) was not associated with an increased risk of toxicity. A dose-dependent effect of the drug on cytotoxicity has been demonstrated in vitro.\textsuperscript{23} Total cumulative dose was originally calculated in the first 498 patients of this series to correlate this variable with the development of pulmonary toxicity. The group of patients developing toxicity had lower cumulative doses administered because these patients correspondingly had a shorter duration of therapy because of their censoring from the study at the time of diagnosis of pulmonary toxicity. Therefore, our approach of analyzing average daily doses both in the loading and maintenance phase of amiodarone therapy was used to circumvent this problem. Although no cases of amiodarone-induced pulmonary toxicity occurred in those patients who received less than 305 mg/day during maintenance therapy in our patient population, toxicity has been reported during low-dose maintenance therapy.\textsuperscript{24} In the present study, because there was no relation between age and drug dose, amiodarone dose was not responsible for the decreased risk seen in the younger patients.

**Plasma Drug Concentrations and Relation to Toxicity**

Measurements of plasma drug concentrations during therapy revealed significantly higher mean desethylamiodarone but not amiodarone concentrations in the group that developed toxicity. A relation between higher amiodarone concentrations and development of drug side effects such as hepatic dysfunction and neuromuscular and ocular effects has been shown previously.\textsuperscript{25,26} but pulmonary toxicity was also shown to occur at lower concentrations.\textsuperscript{26}

It is presently unclear whether desethylamiodarone plays a role in the development of pulmonary toxicity, other than that plasma concentrations tend to correlate with amiodarone doses administered during maintenance therapy.\textsuperscript{14}

**Clinical Implications**

Amiodarone-induced pulmonary toxicity remains a significant complication of therapy with this antiarrhythmic agent and can result in death. Risk may be minimized by administering the lowest effective daily dose of amiodarone during maintenance therapy. The highest risk appears to occur in patients with abnormally low pretreatment pulmonary DLCO values, and this test may identify a higher risk patient for whom closer surveillance may be warranted. A high index of suspicion is often necessary in establishing the diagnosis of pulmonary toxicity, and most cases are reversible if detected early.

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**KEY WORDS**
- pulmonary fibrosis
- diffusion capacity
- pneumonitis
- drug side effect
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