Amiodarone Pulmonary Toxicity: Prospective Evaluation of Serial Pulmonary Function Tests

SHARON A. MAGRO, PAC, E. CLINTON LAWRENCE, MD, SUSAN H. WHEELER, MD, JACK KRAFCHER, MD, HUANG-TA LIN, MD, FACC, CHRISTOPHER R. C. WYNDHAM, MD, FACC

Houston and Dallas, Texas

Pulmonary toxicity developed in 13 (17%) of 89 patients treated with amiodarone during a follow-up period of 2 weeks to 54 (mean 20 ± 15) months. Prospective evaluation of serial pulmonary function tests in 67 patients demonstrated both a significant decrease from baseline in three of six variables in patients with toxicity at the time of diagnosis and a significant difference compared with the same variables in patients without toxicity. The most significant of these was the diffusing capacity for carbon monoxide (D_{L}CO). An individual decrease in D_{L}CO >15% gave an optimal sensitivity of 100% and a specificity of 89% for the diagnosis of pulmonary toxicity. However, a decrease in D_{L}CO >15% did not alone warrant a change in therapy in asymptomatic patients. Although higher maintenance doses of amiodarone appeared to be related to the development of this complication, an abnormal baseline D_{L}CO (<60% of predicted) with or without an initial abnormal chest roentgenogram did not predispose to pulmonary toxicity.

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Amiodarone was first introduced in Europe in 1967 as an antianginal agent and subsequently found to have potent antiarrhythmic properties. Initial reports emphasized its remarkable clinical efficacy in a variety of cardiac arrhythmias. With further experience, however, a variety of adverse effects have become well recognized, of which pulmonary fibrosis remains the most serious because of its potentially life-threatening nature.

Since a possible association between amiodarone and pulmonary fibrosis was first described in 1980 (1), the reported incidence of amiodarone-induced pneumonitis has been highly variable (between 0.5 [2] and 17.6% [3]), a disparity that may be due in part to the lack of established diagnostic criteria. Some investigators (4,5) have attempted to identify potential risk factors for the development of pulmonary toxicity, including preexisting lung disease and pulmonary function abnormalities, but their conclusions have not been supported by others (6).

This study was conducted 1) to define the incidence of pulmonary toxicity in patients treated with amiodarone with use of specified clinical diagnostic criteria, and 2) to determine prospectively the role of pulmonary function testing in the prediction of risk and diagnosis of pulmonary toxicity. Other possible risk factors, including dose, were analyzed in an attempt to identify any patients who might be at special risk for this complication.

Methods

Patient group (Table 1). The total patient group consisted of all 89 consecutive referred patients who were started on oral amiodarone therapy between March 1981 and June 1985 and followed up through July 1986. Prospective follow-up on all 89 patients was complete. The actuarial incidence of pulmonary toxicity and the determination of clinical predictors of this complication were drawn from this total group.

The prospective study of pulmonary function was performed in a cohort drawn from the 89 patients. Fourteen patients did not undergo baseline pulmonary function tests because of frequency of life-threatening arrhythmia (4 patients) or severe congestive heart failure (10 patients); 4 of these 14 patients later developed pulmonary toxicity. In the
remaining 75 patients, analysis of baseline pulmonary function was performed. Eight additional patients did not have follow-up studies because of early death (three patients), severe respiratory distress secondary to amiodarone pulmonary toxicity (three patients) or transfer of clinical care to another institution (two patients). Sixty-seven patients, therefore, completed both baseline and follow-up pulmonary function tests; their clinical characteristics are shown in Table 1 along with those of the total patient group.

Amiodarone dosing. The standard oral loading dose was 1,400 mg/day and was used in 91% of patients. However, this dose ranged between 800 and 1,600 mg/day with a mean loading dose of 1,380 mg/day for the entire group. Duration of loading was 1 to 5 (mean 3) weeks. Both the dose and duration of loading were influenced by the severity of the presenting arrhythmia, the development of adverse effects or the patient's clinical response. The dose was then decreased to 400 to 600 mg/day until the end of the 2nd month of treatment and followed by a maintenance dose of 200 to 600 mg/day (mean 326 mg). Although chosen arbitrarily, this dose was also influenced by the presence of side effects or arrhythmia recurrence. Sixteen patients required concomitant antiarrhythmic therapy for arrhythmia control during amiodarone loading; lidocaine in five patients, procainamide in five, quinidine in three and propranolol in three. Only one patient was discharged on combination therapy (amiodarone and procainamide) with amiodarone being continued alone after 2 months. Three others were subsequently started on a beta-receptor blocking drug in combination with amiodarone; however, only one patient has required chronic low dose therapy with atenolol. During the course of amiodarone therapy, no patient was taking corticosteroids or any drug known to cause pulmonary fibrosis.

Clinical evaluation. For the purpose of this study, initial evaluation before amiodarone therapy included a history and physical examination, chest roentgenogram and pulmonary function tests including a diffusing capacity for carbon monoxide. Other tests performed included a 12 lead electrocardiogram (ECG), 24 h ambulatory ECG monitoring, ophthalmologic examination, radionuclide ventriculography and thyroid and liver function tests. At discharge, all patients were enrolled in a transtelephonic monitoring program to detect the onset of side effects or arrhythmia recurrence between clinic visits. Patients were then followed up in the arrhythmia clinic every 3 months for the 1st year of treatment and every 6 months thereafter. Earlier visits were scheduled if clinically indicated. At discharge and at each follow-up visit, the patient was examined and pulmonary function tests, 24 h ambulatory ECG monitor and laboratory tests were performed.

Pulmonary function tests. Measurements obtained in the pulmonary function laboratory included the 1 s forced expiratory volume (FEV₁), forced vital capacity (FVC), the ratio of FEV₁ to FVC (FEV₁/FVC), total lung capacity (TLC) and the diffusing capacity for carbon monoxide (DLoCO) determined by the modified Krogh technique (single breath method) (7). Arterial blood gases on room air at sea level were also obtained. The FEV₁, FVC, TLC and DLoCO were reported as percent of predicted and the FEV₁/FVC as a ratio expressed as a percentage.

Definitions. Abnormal pulmonary function was defined as <80% of predicted for FEV₁, FVC and TLC and <75% for FEV₁/FVC (8). Abnormal diffusing capacity was defined as <60% of predicted to allow for the wide range of normal seen with this test (7). A partial pressure of oxygen (PO₂) <80 mm Hg with a normal partial pressure of carbon dioxide (PCO₂) was defined as abnormal. A 15% decrease from baseline in any variable was determined to represent a clinically meaningful worsening of pulmonary function. Preexisting restrictive lung disease was defined as a total lung capacity <80% of predicted and preexisting obstructive lung disease as a FEV₁/FVC <75%. A baseline chest roentgenogram was determined to be abnormal in the presence of radiographic evidence of chronic interstitial or obstructive disease of the lungs.

Diagnostic evaluation. In patients with suspected pulmonary toxicity, the diagnostic investigation included hospitalization, chest roentgenogram, pulmonary function testing when possible, gallium-67 lung scanning, bronchoscopy and transbronchial biopsy. Gallium-67 lung scintigraphy was performed 48 h after the intravenous injection of 5 mCi of gallium-67 citrate. Scanning was performed with an Anger scintillation camera and the uptake in lung parenchyma on posterior views scored from 0 to +4 as previously described (9). All gallium-67 lung scans were interpreted and reviewed by an independent expert without knowledge of the patient's clinical history. Amiodarone was discontinued in all patients with suspected toxicity and corticosteroid therapy was instituted in the majority. In an attempt to control recurrence of arrhythmia, some patients were rechallenged with amiodarone either with or without concomitant steroid therapy.

Table 1. Clinical Characteristics of 89 Patients

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<thead>
<tr>
<th>Age (y)</th>
<th>59 ± 11</th>
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<tr>
<td>Coronary artery disease</td>
<td>77 (87%)</td>
<td>57 (65%)</td>
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<tr>
<td>Sustained VT or VF</td>
<td>82 (92%)</td>
<td>63 (96%)</td>
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<tr>
<td>Drugs failed</td>
<td>4 ± 1</td>
<td>4 ± 1</td>
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<tr>
<td>History of congestive heart failure</td>
<td>71 (82%)</td>
<td>51 (78%)</td>
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<tr>
<td>History of pulmonary disease</td>
<td>24 (26%)</td>
<td>16 (24%)</td>
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<tr>
<td>Left ventricular ejection fraction</td>
<td>0.28 ± 0.12</td>
<td>0.28 ± 0.11</td>
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<tr>
<td>Follow-up (months)</td>
<td>20 ± 15</td>
<td>25 ± 14</td>
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VF = ventricular fibrillation; VT = ventricular tachycardia.
Criteria. Our criteria for the diagnosis of pulmonary toxicity required two essential features: 1) dyspnea and cough, and 2) the presence of new or progressive pulmonary infiltrates on chest roentgenogram. In addition, the presence of any two of the following four supporting criteria were required: 1) no response to specific therapy for other possible causes such as congestive heart failure or pneumonia; 2) recovery on discontinuation of amiodarone; 3) recurrence of symptoms on rechallenge; and 4) compatible pulmonary histologic findings.

Statistical analysis. Data were analyzed using the CLINFO data analysis system. Kaplan-Meier methods were used to display the actuarial incidence of pulmonary toxicity. The Student's t test for paired and unpaired data and chi-square analysis with Yates' correction for continuity were used where appropriate. The Wilcoxon non-paired rank sum test was employed where data were not normally distributed. Values are reported as mean ± 1 SD. A probability (p value) ≤0.05 was defined as significant.

Results

Diagnostic criteria. During a follow-up period of 2 weeks to 54 (mean 20 ± 15) months, pulmonary toxicity was diagnosed in 15 of 89 patients, an overall incidence rate of 17%. The probability of developing pulmonary toxicity was 11% after 6 months, 15.5% after 1 year and 19% after 2 years (Fig. 1). The diagnostic criteria fulfilled in these 15 patients were as follows. All patients presented with dyspnea, cough and new pulmonary infiltrates on chest roentgenogram. Before the diagnosis was suspected, seven patients received therapy for congestive heart failure or pneumonia and failed to respond. Amiodarone was discontinued in all 15 patients. Thirteen patients recovered, 10 of whom received prednisone. Two patients died, one of whom had received prednisone late in the course of illness. Six patients were subsequently rechallenged with a lower dose of amiodarone. Four of the six developed recurrence of symptoms despite concomitant steroid therapy in two patients. In 10 of 11 patients, histologic data obtained by transbronchial biopsy or at autopsy were consistent with previously described features of amiodarone pulmonary toxicity (10,11). In the patient without typical histologic findings, the biopsy data were interpreted as indicating organizing pneumonia.

Pulmonary function tests. To assess the role of pulmonary function tests in the diagnosis of pulmonary toxicity, results of such tests were analyzed in the 67 patients who had received both baseline and follow-up studies. Figure 2 shows the percent change from baseline in various pulmonary function tests performed at the time of presentation with symptoms in 8 patients with pulmonary toxicity and at the time of most recent follow-up in 59 patients without pulmonary toxicity. No significant change from baseline in any test occurred in the patients without toxicity. In the patients with diagnosed pulmonary toxicity, all indexes decreased. The 1-s forced expiratory volume (FEV1), PO2, and diffusing capacity for carbon monoxide (Dl CO) demonstrated a clinically meaningful decrease and the forced vital capacity (FVC) a borderline decrease (18.0 ± 24.0%, 16.8 ± 7.0%, 34.3 ± 13.0% and 14.3 ± 13.3%, respectively) compared with baseline, while the FEV1/FVC and total lung capacity (TLC) decreased only 6.4% and 7.0%, respectively, from initial values. The decreases in the FVC, PO2 and Dl CO were significant compared with baseline (p < 0.05, p = 0.001, p = 0.0004, respectively). When the changes in patients with toxicity were then compared with changes in the same indexes in the patients without toxicity, a statistically significant difference was also seen in the FVC, PO2 and Dl CO (p < 0.05, p = 0.004, p < 0.001, respectively).
Thus, patients with toxicity, the FVC, PO₂ and D₂CO demonstrated not only a clinically meaningful and significant decrease from baseline but also a significant difference compared with values in patients who never developed pulmonary toxicity. The decrease in PO₂ does not reflect the marked hypoxia seen in three patients who were too sick to perform pulmonary function tests at the time of presentation with symptoms. The greatest decrease in any index in patients with pulmonary toxicity was the decrease in D₂CO (34.5 ± 13.0%), which was highly statistically different from an increase of 8.6 ± 25.7% in patients without toxicity.

**Gallium-67 lung scan.** A gallium-67 scan of the lungs was positive in 10 of 11 patients, scores ranging from 1+ to 4+ (mean 2+); the uptake was focal in 3 patients and diffuse in 7. Among 12 other patients taking amiodarone who had dyspnea and cough due to causes other than amiodarone (heart failure in 9, pneumonia in 2 and recurrent pulmonary emboli in 1), the gallium-67 scan was negative in each (p < 0.001). Thus, the sensitivity of a positive gallium-67 lung scan for the diagnosis of pulmonary toxicity was 91%, the specificity of the test was 100% and the predictive value of a positive test in this group of patients receiving amiodarone was 100%.

**Potential risk factors.** One objective of this study was to identify any potential risk factors for the development of pulmonary toxicity. The distribution of pulmonary toxicity in the 15 patients was first examined according to duration of therapy. Eleven patients (73%) developed symptoms within the first 7 months of treatment. In three of these patients, the first signs of toxicity appeared during the loading period at 13, 15 and 30 days of treatment with 1,400 mg/day of amiodarone. The clinical status of these patients deteriorated rapidly, and they required intubation and mechanical ventilation within 3 to 10 days after the onset of symptoms. Seven of the remaining eight patients developing early toxicity were receiving a maintenance dose of 600 mg/day and one was receiving a dose of 400 mg/day. Of the four patients who developed pulmonary toxicity later in the course of treatment, all but one, receiving 200 mg/day, were receiving a maintenance dose of 400 mg/day at the time of presentation with symptoms. However, two of these four (who developed toxicity at 15 and 28 months, respectively) had been receiving a higher maintenance dose or 400 mg and 600 mg/day, respectively, for recurrent ventricular tachycardia and had received an arbitrary dose reduction only shortly before the onset of symptoms.

This unusually high incidence of pulmonary toxicity during the early months of treatment with amiodarone prompted us to look more closely at the relation between dose and duration of therapy. Analysis of the maintenance dose at 3 and 6 months of treatment demonstrated that, at both time intervals, the patients with subsequent toxicity were taking a significantly higher daily dose than were the patients who never developed toxicity. At 3 months, the former group was receiving a mean maintenance dose of 527 ± 101 mg/day compared with the latter patients, who were taking 431 ± 133 mg/day (p = 0.02). At 6 months this difference remained significant: 513 ± 125 mg/day in the patients who later developed toxicity compared with 360 ± 143 mg/day in the remaining patients (p = 0.01). Cumulative dose was also analyzed: at 3 months, the cumulative dose was 70 ± 15 g in patients who later developed pulmonary toxicity and 62 ± 13 g in those who did not (p = NS). At 6 months, the cumulative dose was 111 ± 19 and 95 ± 21 g, respectively (p < 0.05), reflecting the fact that patients with toxicity had received higher maintenance doses for a longer period of time. In these patients, the cumulative dose ranged from 30.4 to 303.6 g (122 ± 81.8) at the time of diagnosis.

Other potential risk factors did not differentiate the patients who became toxic from those without toxicity; these included age, left ventricular ejection fraction, history of congestive heart failure or cigarette smoking, total loading dose in grams, loading dose in mg/kg per day or duration of loading (Table 2). In particular, a history of pulmonary disease or an abnormal chest roentgenogram was no more prevalent in patients with than in those without pulmonary toxicity.

**Baseline pulmonary function also did not differ significantly between these two groups in the 75 patients who underwent pulmonary function tests before amiodarone therapy (Fig. 3).** On the basis of these studies, preexisting obstructive lung disease was present in 31 (48%) of 64 patients without pulmonary toxicity and in 5 (46%) of 11 patients with toxicity (p = NS). The incidence of restrictive lung disease was also similar in the two groups (16% versus 20%, respectively). Baseline values for diffusing capacity for carbon monoxide (D₂CO) were also comparable: a mean of 66 ± 21% of the predicted value in the former patients and 68

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<th>Table 2. Potential Risk Factors in 89 Patients*</th>
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<tr>
<td>Patients Without Toxicity</td>
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<tr>
<td>Age (yr)</td>
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<tr>
<td>History of congestive heart failure (% patients)</td>
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<tr>
<td>Left ventricular ejection fraction</td>
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<td>History of cigarette smoking (% patients)</td>
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<td>Loading dose</td>
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<td>Duration of loading (days)</td>
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<td>History of pulmonary disease (% patients)</td>
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<td>Abnormal chest roentgenogram (% patients)</td>
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*All p = NS.
Fifteen (15%) of 73 patients had both an abnormal baseline DLCO and chest roentgenogram and none of these patients developed pulmonary toxicity. Thus, abnormal baseline pulmonary function including an abnormal DLCO either alone or in combination with an initial abnormal chest roentgenogram did not predict the development of pulmonary toxicity.

**Diagnostic value of decrease in DLCO between two tests** (Table 3). Because a decrease in diffusing capacity for carbon monoxide (DLCO) was the most striking laboratory finding at the time of diagnosis, we analyzed the diagnostic value of a decrease in DLCO between any two successive tests. Two hundred eighty-six pulmonary function tests, including 67 baseline tests and 219 follow-up tests, were analyzed in the 67 patients. Decreases of 15, 20, and 30% were tested as a marker of toxicity. Of the 18 follow-up tests performed in the eight patients who later developed pulmonary toxicity, none demonstrated a significant decrease in DLCO until the time of diagnosis. That is, 10 of these follow-up tests were performed at a time when pulmonary symptoms were absent and were considered to be non-diagnostic as were the 201 follow-up tests performed in the 59 patients without pulmonary toxicity. Maximal sensitivity of 100% was obtained with a ≥15% decrease and maximal specificity of 98% with a ≥30% decrease. As expected, intermediate sensitivity and specificity were associated with a ≥20% decrease. The positive diagnostic value of a decrease in DLCO of ≥15, 20 or 30% was 25, 37 and 60%, respectively. On the other hand, the probability that a patient with <15% decrease in DLCO had pulmonary toxicity was extremely low (negative diagnostic value 100%). Compared with the DLCO, none of the other pulmonary function tests yielded a similar sensitivity, specificity or diagnostic accuracy for the diagnosis of pulmonary toxicity.

**Discussion**

Diagnosis of pulmonary toxicity. Pulmonary fibrosis is now a well recognized complication of amiodarone therapy. Its reported incidence, although variable, has remained generally low. The diagnosis of amiodarone-induced pulmonary toxicity is difficult, with findings often indistinguishable from those of congestive heart failure or pneumonia. Although it is generally accepted that this syndrome is characterized by dyspnea, cough, pulmonary infiltrates, restrictive changes on pulmonary function testing and compatible histologic findings, the diagnosis has often been made retrospectively and by exclusion of alternative causes. Without a high index of suspicion for its recognition and specified criteria on which to base the diagnosis, symptoms or death in individual patients may be ascribed to progressive heart failure or respiratory infection and the real incidence underestimated. On the other hand, a diagnosis of pulmonary toxicity based on less than stringent criteria could lead to the premature discontinuation of amiodarone and loss of potential long-term benefit in the group of patients who most likely need it the most. For example, in one other prospective study in which diagnostic criteria were defined, Kudenchuk et al. (5) diagnosed pulmonary toxicity by new or worsening interstitial infiltrates on chest roentgenogram associated with worsening measurements of total lung or diffusing capacity, with or without pulmonary symptoms; they recommended dose reduction or discontinuation of amiodarone even in asymptomatic patients meeting these criteria. Such asymptomatic patients were also included in two smaller reported series (3,12), raising the interesting possibility that a detectable subclinical phase of the illness may occur. In the
present study we regarded the presence of pulmonary symptoms as one of two essential criteria in determining the diagnosis. Future agreement among clinicians regarding diagnostic criteria would facilitate the early recognition and accurate diagnosis of this complication and thus help establish the real incidence.

**The role of pulmonary function testing in the diagnosis of pulmonary toxicity.** This role has not been examined in previous reports. Of three prospective studies reporting the results of serial pulmonary function tests (5,6,13), none examined the potential diagnostic value of such studies. Although Adams et al. (13) noted a small overall decrease in DLCO in 34 patients after 3 months of amiodarone therapy, both Kudenchuk (5) and Rakita (6) and coworkers found no significant change in mean pulmonary function test measurements before and after amiodarone therapy in their patient population as a whole. A similar analysis of our data supports the latter findings; mean values before and after amiodarone therapy for FEV₁, FVC, FEV₁/FVC, TLC, PO₂, and DLCO were unchanged. However, an analysis of the same variables first compared before and after therapy in patients with pulmonary toxicity and then compared between patients with and without toxicity revealed striking differences in three of the six variables, the most significant of which was in the diffusing capacity for carbon monoxide (DLCO). In an attempt to assess the diagnostic accuracy of this marked decrease in DLCO in patients with pulmonary toxicity, we found an optimal sensitivity of 100% and a specificity of 89% associated with a decrease in DLCO of >15% between any two successive tests. At the time intervals used in this study, however, serial measurements of DLCO did not demonstrate that a decrease was an early marker of the later development of pulmonary toxicity. Rather, in patients with respiratory symptoms and new or progressive pulmonary infiltrates, a meaningful worsening of DLCO occurred in all patients whose diagnosis was later confirmed by supporting criteria.

*On the other hand, to depend on a meaningful decrease in DLCO alone to make an accurate diagnosis of pulmonary toxicity has limitations.* We found that, although a 15% decrease in DLCO was demonstrated at any one determination in 30 of 67 patients, 22 of these patients never developed clinically evident pulmonary toxicity (Table 3). Fourteen of these 22 patients had a subsequent improvement in DLCO to baseline value, and the other 8 patients remained clinically asymptomatic with a decreased but stable DLCO at the time of their last follow-up (mean 8 months later). The clinical significance of a stable but chronic reduction in DLCO in asymptomatic patients is uncertain; on the other hand, transient decreases in DLCO may largely reflect individual variability and emphasize the nonspecificity of the DLCO itself (8). This variability was also observed by Rakita et al. (6), who evaluated 170 serial pulmonary function tests in 35 patients and found a “marked variation in individual test results in any one patient over time.” In the series of Kudenchuk et al. (5), 19 (28%) of 69 patients developed a ≥15% decrease in diffusing capacity after treatment, 11 of whom did not develop pulmonary toxicity. Although Kudenchuk et al. suggested that dose reduction or discontinuation at first notice of a worsening DLCO or total lung capacity (TLC) even without radiologic changes might abort the onset or reduce the severity of amiodarone pulmonary toxicity, our follow-up indicates that a change in therapy is not warranted on that basis alone. A meaningful reduction in DLCO alone should alert the investigator to the possibility of pulmonary toxicity but should be interpreted as an indication for closer follow-up with further diagnostic studies to be performed as indicated. We suggest that when pulmonary symptoms are associated with a meaningful decrease in DLCO, a gallium-67 scan may further differentiate patients with pulmonary toxicity from those with pulmonary symptoms of other causes.

**Gallium-67 scintigraphy.** This test, performed in 11 of 15 patients with pulmonary toxicity, revealed abnormal pulmonary gallium-67 uptake in 10. Van Roolij et al. (14) reported that in three cases of amiodarone pneumonitis pulmonary gallium-67 uptake occurred in all. Although the gallium-67 scan is not diagnostic for a particular pulmonary disorder, there is evidence that it is sensitive to and specific for the alveolitis of pulmonary interstitial disease (15). The test is widely available and noninvasive and we found it extremely useful in differentiating, with high sensitivity and specificity, heart failure from pulmonary involvement due to amiodarone. Prospective clinical studies correlating the gallium-67 scan with development of pulmonary toxicity may further confirm the diagnostic value of this test.

**X-ray findings.** By study design, the diagnosis of pulmonary toxicity was based in part on chest roentgenographic findings. Thus, we are unable to state the value of serially performed chest roentgenograms as an early indicator of pulmonary toxicity. It is possible that serial chest roentgenograms might have provided important information and that early preclinical changes may predate changes in the DLCO. However, the chest roentgenogram has been shown to be neither a sensitive nor a specific monitor of the alveolitis of interstitial lung disease (15).

**Present protocol for diagnostic testing and criteria.** As a result of the present study, we continue to perform and strongly recommend complete pulmonary function testing, including a diffusing capacity for carbon monoxide (DLCO) before initiation of amiodarone therapy and whenever pulmonary toxicity is suspected. It was disappointing that changes in serial pulmonary function did not presage the development of pulmonary toxicity; for that reason, with the exception of the DLCO, we no longer perform these studies during routine follow-up evaluation. However, some assess-
The present study suggests that the Dl CO and gallium-67 scanning have diagnostic value. As a result, we have expanded our diagnostic criteria to include a meaningful reduction in diffusing capacity and a positive gallium-67 scan in the presence of pulmonary symptoms and new or progressive pulmonary infiltrates on chest roentgenogram. Three proposed major criteria and five supporting criteria are summarized in Table 4. It is suggested that all three of the major criteria be satisfied and that two or more of the supporting criteria be present to confirm the diagnosis.

Potential risk factors. One main objective of this study was to attempt to identify any baseline clinical or laboratory characteristic that might have predicted the occurrence of amiodarone pulmonary toxicity. Several variables that were found not to be indicative of risk in this patient group included age, history of congestive heart failure or cigarette smoking, left ventricular ejection fraction, total loading dose in grams, loading dose in mg/kg per day and duration of loading. Higher maintenance doses did appear to be related to the development of pulmonary toxicity. This is the first demonstration of a relation previously suggested by other investigators (10,16-18). The significant difference in cumulative dose at the 6 month time interval between patients with and without pulmonary toxicity was more likely a reflection of the higher maintenance doses taken by patients who later developed pulmonary toxicity than an independent factor predisposing a patient to risk, because the range of cumulative dose at the time of diagnosis was so wide (30.4 to 303.6 g). The fact that pulmonary toxicity can occur abruptly and without warning during the loading phase or late in the course of treatment on smaller maintenance doses suggests that factors in addition to dose contribute to the development of this complication. However, until the mechanism is further understood, establishing patients on the lowest effective maintenance dose within the first several months of treatment may reduce the incidence of pulmonary toxicity.

As a result of this study we have modified our dosing schedule. A loading dose of 1,000 mg/day for 2 weeks is followed by a stepwise decrease in dose in an attempt to reach a maintenance dose of 200 to 400 mg at the end of the 3rd month of treatment. Whether this procedure will significantly decrease the incidence of pulmonary toxicity at our institution will only be confirmed by time.

The presence of preexisting pulmonary disease or initial abnormalities on chest roentgenogram or Dl CO as independent predictors of risk of pulmonary toxicity is controversial. Greene et al. (4) reported that preexisting chronic lung disease with depression of diffusing capacity for carbon monoxide weakly predicted which patients would develop pulmonary complications. In a subsequent report from the same institution, Kudenchuk et al. (5) not only stated that initial abnormalities on chest roentgenogram or diffusing capacity were predictive of risk of pulmonary toxicity but also recommended that patients with these abnormalities be considered for alternative therapy. Other investigators (19-31) have endorsed this point of view, but our data do not support their recommendation. We found no evidence that preexisting lung disease or baseline chest roentgenogram or Dl CO abnormalities, either alone or in combination, were predictive of risk of developing pulmonary toxicity. Although our laboratory definition of an abnormal Dl CO (<60% of predicted) differed from that of Kudenchuk et al. (<80% of predicted), our results when analyzed similarly remain unchanged. Our finding was consistent with that of Rakita et al. (6), who found no supportive evidence for the risk of pulmonary toxicity based on initial values in pulmonary function. Our conclusion is further supported by extended follow-up in patients without pulmonary toxicity since the completion of this formal study. Of the 62 patients in this group who had baseline Dl CO measurements, 35 of whom had preexisting abnormalities in Dl CO or chest roentgenogram or a history of pulmonary disease, none to date has developed pulmonary toxicity during a follow-up period that now extends to 35 ± 19 months. Thus, with careful clinical follow-up, there is no reason that amiodarone cannot be given safely to most patients regardless of preexisting pulmonary status.

The importance of the recognition and diagnosis of pulmonary toxicity, however, cannot be overemphasized, especially in view of the recent approval of amiodarone for life-threatening ventricular arrhythmias. On the other hand, to withhold or withdraw potentially lifesaving therapy from patients frequently resistant to all other available anti-
arrhythmic medications based on preexisting pulmonary abnormalities or a reduction in pulmonary function alone does not appear to be justified in the case of amiodarone.

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References


