Bronchoalveolar Lavage Cell Count and Differential Are Not Reliable Indicators of Amiodarone-induced Pneumonitis*

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Amiodarone-induced interstitial pneumonitis is a serious, frequently fatal untoward effect of a commonly used antiarrhythmic agent. Recent reports suggest that bronchoalveolar lavage (BAL) fluid cellular analysis might be used to diagnose amiodarone-induced pneumonitis. The purpose of this study was to determine if the diagnosis of amiodarone-induced pneumonitis could be made by patient history, pulmonary function evaluation, and examination of BAL fluid. We studied five groups of patients. Three of the five groups received amiodarone: patients receiving amiodarone without evident lung toxic reaction, patients with amiodarone-induced pneumonitis, and amiodarone-treated patients diagnosed as having other pathologic processes involving the lung. The two other groups examined were healthy volunteers and patients with interstitial lung disease from causes other than amiodarone. Pulmonary function tests included vital capacity (FVC), first second forced exhaled volume (FEV1), total lung capacity (TLC), and diffusing capacity for carbon monoxide (Dco). BAL fluid analysis included total and differential cell counts. We found that amiodarone-induced interstitial pneumonitis was not associated with an alteration in pulmonary function or BAL cellular composition which could permit its distinction from amiodarone-treated patients diagnosed as having an unrelated pulmonary process or patients with interstitial lung disease from other causes. The most frequent abnormality encountered in patients with amiodarone toxicity was a reduction in the percentage of macrophages in the differential cell count. The sensitivity, specificity, and predictive value of this finding was 82 percent, 69 percent, and 69 percent, respectively. The sensitivity, specificity, and predictive value of a ≥15 percent reduction in Dco was 44 percent, 50 percent, and 36 percent, respectively. We conclude that amiodarone-induced interstitial pneumonitis remains a diagnosis of exclusion, and the role of BAL fluid analysis is to narrow the differential diagnosis through microbiologic culture and cytologic examination.

(Chest 1992; 102:999-1004)

CHF = congestive heart failure; ICD = implantable cardioverter defibrillator; ILD = interstitial lung disease

Amiodarone has been used since 1969 in the United States for treatment of ventricular arrhythmias that were refractory to other treatments. A serious complication of therapy has been pulmonary toxic reactions that are reported to occur in 3 to 27 percent of amiodarone-treated patients.1 The mortality from amiodarone-induced pneumonitis is estimated to be as high as 23 to 33 percent.1,2 Discontinuation of amiodarone therapy in cases of suspected toxicity can also be hazardous because of reemergence of ventricular arrhythmias.3 More recently, implantable cardioverter defibrillators (ICD) have been used when amiodarone therapy must be discontinued. However, reports of postoperative noncardiogenic pulmonary edema among amiodarone-treated patients illustrate an additional risk.4,7 Accurate diagnosis of amiodarone-induced pneumonitis is important. Unfortunately, it is also quite difficult. Patients treated with amiodarone commonly have coexistent congestive heart failure (CHF) and obstructive airways disease (COPD). Many of the patients receiving amiodarone therapy are smokers or former smokers, which can result in variable degrees of pulmonary function abnormalities before and during amiodarone therapy. Common symptoms of amiodarone-induced pulmonary toxicity are dyspnea, cough, fever, pleuritic chest pain, malaise, and weight loss. These symptoms are nonspecific and are also consistent with exacerbations of both COPD and CHF.

Attempts have been made to find a sensitive and specific test for amiodarone-induced pulmonary toxicity. From 1982 to 1985, reports appeared that phospholipid-laden "foamy" macrophages in bronchoalveolar lavage (BAL) fluid might be diagnostic for amiodarone-induced interstitial pneumonitis.8-10 Subsequent reports of clinical and pathologic correlations established that these changes were present not only in toxic patients but also in asymptomatic patients taking amiodarone.11-13 More recently, Akoun et al14,15 have postulated that amiodarone-induced pulmonary toxicity is a form of hypersensitivity pneumonitis based on their finding of increased number of lymphocytes with a reverse in T4/T8 in BAL fluid. Akoun

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et al.\textsuperscript{16} suggested that BAL may be used to accurately diagnose amiodarone-induced interstitial pneumonitis. Other investigators, however, have found nonspecific increases in the numbers of neutrophils and macrophages in BAL.\textsuperscript{13,17-21}

To determine the validity of these observations, we performed BAL on three groups of amiodarone-treated patients; asymptomatic volunteers receiving amiodarone (nontoxic), patients with amiodarone-induced pneumonitis (toxic), and patients suffering from a pulmonary process unrelated to their amiodarone-treatment (sick). Two groups of patients not treated with amiodarone were examined similarly: healthy volunteers (controls) and patients with interstitial lung disease from other causes (ILD). BAL fluid cell count and differential cell count in the three amiodarone-treated and two untreated groups were analyzed and compared. We also analyzed pulmonary function at the initiation of amiodarone treatment and at the time of bronchoscopy and the relationship of BAL fluid cell counts to daily dose, cumulative dose, and duration of therapy in the three amiodarone-treated groups.

METHODS

\textbf{Patient Selection}

Patients were enrolled in the study under a protocol reviewed and approved by the Institutional Review Board at St. Louis (Mo) University. Toxic, ILD, and sick patients were referred to the Division of Pulmonology and Pulmonary Occupational Medicine for definitive diagnosis and treatment. Nontoxic amiodarone-treated volunteers were recruited from the arrhythmia service outpatient clinic. Normal healthy hospital staff volunteers served as control subjects.

\textbf{Amiodarone Treatment Protocol}

Many of the amiodarone-treated patients examined in this study were enrolled under a compassionate use preclinical amiodarone drug study and were followed up prospectively for up to eight years. Informed consent was obtained from all patients prior to initiation of the drug therapy. Patients were begun on a regimen of intravenous amiodarone because of frequent sustained ventricular tachycardia unresponsive to conventional therapy with intravenous antiarrhythmic medications. Oral amiodarone therapy was begun in patients who did not respond to conventional oral antiarrhythmic therapy for recurrent sustained monomorphic ventricular tachycardia or ventricular fibrillation. Patients initially receiving intravenous amiodarone were given 1,200 to 2,000 mg/day for three to seven days. Oral amiodarone therapy was then begun at 200 to 1,200 mg/day. Patients initially begun on a regimen of oral amiodarone therapy received a loading dose of 500 to 1,200 mg/day with a similar tapering sequence. As part of the protocol, patients had full pulmonary function tests, including standard spirometry, lung volumes, and diffusing capacity for carbon monoxide. Patients had baseline pretreatment pulmonary function tests and follow-up tests at the time of bronchoscopy. Pretreatment pulmonary function tests were not performed in patients who received intravenous amiodarone but were obtained as soon as the patient was clinically stable. Tests were performed on a water seal spirometry system (Collins DS 560). Lung volumes were measured both by helium dilution and body plethysmography. Instruments were calibrated daily with a 3-L syringe. Calibration criteria met or exceeded American Thoracic Society guidelines.

\textbf{Toxicity Criteria}

The diagnosis of amiodarone-induced pulmonary toxicity was made by a combination of clinical and pathologic criteria. Clinical criteria included the development of a new or progressing infiltrate on chest roentgenogram, complaints of dyspnea, and physical findings of rales and tachypnea without other clinical evidence for pneumonia or congestive heart failure. Clinical criteria for infectious pneumonia included new focal infiltrate on chest roentgenogram, fever, elevated white blood cell count, and purulent sputum production with bacteria evident on Gram stain. Criteria for congestive heart failure included leg edema, the presence of neck vein distention, and an S3 gallop. For diagnosis of amiodarone-induced lung toxicity, patients displayed at least two of the three clinical toxicity variables and had compatible histologic features on lung biopsy specimens. Lung biopsy specimens, either open lung or transbronchial, showing interstitial fibrosis on a trichome stain of the histologic specimen fulfilled pathologic criteria. Interstitial widening with edema and inflammatory cells, with or without type 2 cell hyperplasia or atypia, was also accepted.

\textbf{Bronchoalveolar Lavage}

Bronchoalveolar lavage was performed with a fiberoptic bronchoscope (Olympus BF-10) wedged into a right middle lobe subsegmental bronchus in volunteers. The segment most involved by an acute process evident roentgenographically was lavaged in toxic, ILD, and sick patients. Three 50-ml aliquots of sterile nonbacteriostatic saline solution were instilled and withdrawn through the biopsy port of the bronchoscope. Aliquots were pooled and transported on ice to the laboratory. A 10-ml aliquot of BAL fluid was removed and pipetted into a hemocytometer for measurement of total cell count. A 100-ml aliquot of BAL fluid diluted with 100 ml of Hanks balanced salt solution with 2 percent bovine serum albumin was spun at 700 rpm × 2 min in a centrifuge (Shandon Cytospin II). Slides were allowed to air dry and were stained with a modified Wright's stain. Three hundred cells were counted and results were expressed as percentages of macrophages, lymphocytes, polymorphonuclear leukocytes, and eosinophils.

\textbf{Statistical Methods}

Values for the total number of cells per microliter and number and percentage of total cells classified as macrophages, lymphocytes, neutrophils, and eosinophils were compared for the five groups: toxic, nontoxic, controls, ILD, and sick by analysis of variance (ANOVA). Significance of the differences determined by ANOVA was evaluated by Hochberg's GT\textsubscript{2} test for unplanned comparison among means.\textsuperscript{22} Mean duration of therapy and cumulative and daily dose of amiodarone were analyzed in toxic, sick, and nontoxic patients by ANOVA. The pulmonary function (FFT) variables, forced vital capacity (FVC), forced expiratory volume in the first second (FEV\textsubscript{1}), total lung capacity (TLC), and diffusing capacity for carbon monoxide (Dco) and their percentage predicted values were analyzed in the groups of toxic, sick, and nontoxic patients. FFT variables at the start of amiodarone treatment and at the time of bronchoscopy were analyzed by ANOVA for the three groups: toxic, sick, and nontoxic. Changes in pulmonary function during amiodarone treatment were evaluated by subtraction of FFT variables obtained at the time of bronchoscopy from baseline pretreatment values and by calculating percentage of change. Percentage of change was calculated by using the following formula: (baseline value-follow-up value)/baseline value × 100. Mean values for differences in FVC, FEV\textsubscript{1}, TLC, Dco, and for differences in the predicted values for these variables were compared by ANOVA for the three amiodarone-treated groups.

Daily dose, cumulative dose, and duration of amiodarone therapy were correlated with the number of cells and the differential cell counts in the BAL fluids of toxic and nontoxic patients by linear regression. All values are expressed as mean ± standard error. A p
value of <0.05 was considered significant. An r value of ≥0.9 was considered to represent a strong correlation. R values ≥0.6 but ≤0.9 were considered to represent a moderate correlation.

RESULTS

Patient Demographics and Number

Thirteen amiodarone-treated but clinically nontoxic patients volunteered to participate in this study. Seventeen amiodarone-treated referrals were evaluated for diagnosis and treatment of suspected amiodarone toxicity. Eleven of these fulfilled clinical and pathologic criteria for amiodarone toxicity. Six were diagnosed as having other pathologic processes affecting the lung. These included congestive heart failure (two), sarcoidosis (two), pneumonia (one), and anaphylaxis with noncardiogenic pulmonary edema (one). In the nontoxic group, three (23 percent) were smokers and six (46 percent) had quit smoking at least six months before BAL. Three (27 percent) of the 11 toxic patients were smokers and seven (64 percent) had quit at least six months before BAL. Among the sick patients, there was one (17 percent) smoker and two former smokers. There was one woman each in the toxic and nontoxic groups and two women in the sick group. The mean ages for toxic, nontoxic, and sick patients were 62 ± 3.4 years, 58 ± 4.8 years, and 67.5 ± 4.9 years, respectively. All 53 healthy controls were nonsmokers. Of the 27 ILD patients, 12 had sarcoidosis, five had connective tissue diseases, four were idiopathic, and two each were diagnosed as having silicosis, lymphoma, and eosinophilic syndromes.

Amiodarone Dose and Duration of Treatment

The mean daily amiodarone dose at the time of BAL was similar for each of the three amiodarone-treated groups (Table 1). The cumulative dose, calculated by daily dose in milligrams times the duration in months, was significantly higher in sick patients than in toxic patients. No significant difference in cumulative dose was found between toxic and nontoxic patients. No significant difference was found in duration of therapy among the three amiodarone-treated groups.

Dose and Duration of Treatment Compared with BAL Cells

Linear regression revealed that no correlation was found between daily amiodarone dose or duration and BAL cell counts or differential cell counts in amiodarone-treated nontoxic and sick patients. Several moderate correlations were found in amiodarone toxic patients. The lymphocyte count in BAL expressed as cells per microliter was moderately related to cumulative dose and the duration of drug treatment (p = 0.05; r = 0.61 and 0.75, respectively). The percentage of the BAL differential cell count designated as lymphocytes was found to be related to the duration of amiodarone therapy (p = 0.04; r = 0.61) and the percentage of neutrophils was related to daily dose p = 0.03; r = 0.66).

Pulmonary Function Tests

Pretreatment FVC, FEV₁, FEV₁/FVC, TLC, Dco, and their respective percent predicted values were not significantly different for amiodarone-treated toxic, nontoxic, and sick patients (Table 2). Follow-up ventilatory variables were also not different for the three amiodarone-treated groups except for Dco (Table 2), which was significantly lower in the sick group compared with the nontoxic group. Follow-up Dco for toxic patients was not significantly different from nontoxic patients. FVC, FEV₁, FEV₁/FVC, TLC, and Dco varied similarly among the three amiodarone-treated groups over time. There was no significant fall in any of the ventilatory variables from baseline for any of the amiodarone-treated groups when compared with follow-up values.

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Table 1—Amiodarone Dose*

<table>
<thead>
<tr>
<th></th>
<th>Daily Dose, mg/day</th>
<th>Cumulative Dose, mg/day × mo</th>
<th>Duration, mo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nontoxic (n = 13)</td>
<td>262 ± 33</td>
<td>10,102 ± 1,871</td>
<td>34 ± 6</td>
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<tr>
<td>Toxic (n = 11)</td>
<td>382 ± 86</td>
<td>6,518 ± 1,879</td>
<td>20 ± 5</td>
</tr>
<tr>
<td>Sick (n = 5)</td>
<td>500 ± 63</td>
<td>16,760 ± 3,474</td>
<td>48 ± 11</td>
</tr>
<tr>
<td>Significance</td>
<td>NS</td>
<td>p &lt; 0.05</td>
<td>NS</td>
</tr>
</tbody>
</table>

*Values expressed as mean ± standard error.

Table 2—Pulmonary Function Variables*

<table>
<thead>
<tr>
<th></th>
<th>Nontoxic (n = 12)</th>
<th>Toxic (n = 11)</th>
<th>Sick (n = 5)</th>
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</thead>
<tbody>
<tr>
<td>Baseline</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>FVC, L</td>
<td>3.7 ± 0.21</td>
<td>3.61 ± 0.27</td>
<td>3.16 ± 0.43</td>
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<tr>
<td>FVC, % predicted</td>
<td>84 ± 5.4</td>
<td>79 ± 6.4</td>
<td>80 ± 6.4</td>
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<tr>
<td>FEV₁, L</td>
<td>2.58 ± 0.16</td>
<td>2.74 ± 0.24</td>
<td>2.29 ± 0.25</td>
</tr>
<tr>
<td>FEV₁, % predicted</td>
<td>84 ± 5.4</td>
<td>85 ± 7.4</td>
<td>82 ± 6.4</td>
</tr>
<tr>
<td>FEV₁/FVC, %</td>
<td>72 ± 3.3</td>
<td>75 ± 3.3</td>
<td>75 ± 5.3</td>
</tr>
<tr>
<td>TLC, L</td>
<td>6.48 ± 0.3</td>
<td>5.97 ± 0.44</td>
<td>5.53 ± 0.82</td>
</tr>
<tr>
<td>TLC, % predicted</td>
<td>97 ± 5.6</td>
<td>96 ± 6.6</td>
<td>90 ± 7.6</td>
</tr>
<tr>
<td>Dco, ml/min/mm Hg</td>
<td>22 ± 3.1</td>
<td>17 ± 2.1</td>
<td>15 ± 2.5</td>
</tr>
<tr>
<td>Dco, % predicted</td>
<td>87 ± 10.0</td>
<td>64 ± 7.4</td>
<td>67 ± 10.4</td>
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</tbody>
</table>

Follow-up

<table>
<thead>
<tr>
<th></th>
<th>Nontoxic (n = 11)</th>
<th>Toxic (n = 9)</th>
<th>Sick (n = 5)</th>
</tr>
</thead>
<tbody>
<tr>
<td>FVC, L</td>
<td>3.4 ± 0.2</td>
<td>3.1 ± 0.3</td>
<td>2.6 ± 0.3</td>
</tr>
<tr>
<td>FVC, % predicted</td>
<td>78 ± 4.4</td>
<td>70 ± 7.6</td>
<td>66 ± 6.6</td>
</tr>
<tr>
<td>FEV₁, L</td>
<td>2.55 ± 0.2</td>
<td>2.17 ± 0.3</td>
<td>1.83 ± 0.2</td>
</tr>
<tr>
<td>FEV₁, % predicted</td>
<td>84 ± 5.4</td>
<td>71 ± 9.9</td>
<td>67 ± 3.7</td>
</tr>
<tr>
<td>FEV₁/FVC, %</td>
<td>76 ± 3.3</td>
<td>69 ± 5.4</td>
<td>74 ± 5.4</td>
</tr>
<tr>
<td>TLC, L</td>
<td>6 ± 0.2</td>
<td>5.6 ± 0.6</td>
<td>4.5 ± 1.2</td>
</tr>
<tr>
<td>TLC, % predicted</td>
<td>88 ± 3.3</td>
<td>82 ± 7.4</td>
<td>71 ± 10.0</td>
</tr>
<tr>
<td>Dco, ml/min/mm Hg</td>
<td>21 ± 2.1</td>
<td>15 ± 2.1</td>
<td>10 ± 3.1</td>
</tr>
<tr>
<td>Dco, % predicted</td>
<td>80 ± 8.0</td>
<td>59 ± 8.4</td>
<td>38 ± 12.4</td>
</tr>
</tbody>
</table>

*Values expressed as mean ± standard error.

tp < 0.05 vs nontoxic.
Sensitivity, Specificity, and Predictive Value of \( \text{DCO} \)

For the purpose of this study, we arbitrarily defined a \( \geq 15 \)% change in any ventilatory variable as a significant decrease. Four of nine toxic patients had a \( \geq 15 \)% decrease in \( \text{DCO} \) from pretreatment values. (Two toxic patients were unable to perform follow-up pulmonary function testing because of the severity of their illness.) Therefore, in our population, \( \text{DCO} \) had a 44% sensitivity in diagnosing amiodarone-induced pneumonitis. Seven of 14 in both groups had a \( \geq 15 \)% decrease in \( \text{DCO} \) from pretreatment values, resulting in a 50% specificity for the \( \text{DCO} \) criterion. The predictive value of the \( \text{DCO} \) was 36 percent.

**BAL Cell Counts**

The total number of cells per microliter in all three amiodarone-treated groups was not significantly different from control subjects or the ILD group (Table 3). Total numbers of macrophages were significantly increased in the ILD group compared with control subjects. The percentage of cells identified as macrophages was significantly reduced in the toxic, sick, and ILD groups compared with control subjects. The mean percentage of macrophages for the sick and ILD groups was also significantly lower than in the nontoxic group. The toxic, sick, and ILD groups all had a significantly greater percentage of neutrophils in the differential cell count of BAL than did the control subjects. The ILD group had a greater percentage of eosinophils than did the control group.

Patients with amiodarone-induced pneumonitis (toxic) had a greater percentage of neutrophils and a lesser percentage of macrophages in the differential cell count compared with control subjects. Amiodarone-treated patients examined for a pulmonary process unrelated to amiodarone (sick) had BAL fluid cell count abnormalities similar to those with amiodarone-induced pneumonitis. Both demonstrated decreased percentage of macrophages and increased percentage of neutrophils in the differential cell count. However, the total number of lymphocytes per microliter of BAL fluid was lower in the sick group than the toxic group. In summary, no single or combination of BAL variables distinguished the toxic group from the nontoxic or sick groups.

**DISCUSSION**

The purpose of this study was to determine if the diagnosis of amiodarone-induced pneumonitis could be made reliably with patient history, pulmonary function evaluation, and by examination of BAL fluid. We compared BAL fluid cells, pulmonary function variables, amiodarone dose, and duration of therapy in three groups of amiodarone-treated patients (toxic, sick but not toxic, nontoxic). BAL fluid cell counts and differential cell counts from the three amiodarone-treated groups were compared with two groups of patients not taking amiodarone; healthy volunteers (controls) and patients examined for ILD from other causes.

We previously reported that pulmonary function variables, including \( \text{DCO} \), were not helpful in establishing the diagnosis of amiodarone-induced pneumonitis.\(^{31}\) Several investigators have found \( \text{DCO} \) to be a sensitive test for amiodarone-induced interstitial pneumonitis.\(^{24-27}\) However, predictive value of \( \text{DCO} \) may be poor. We found \( \text{DCO} \) to be neither a sensitive nor specific test for amiodarone-induced interstitial pneumonitis. The differences in sensitivity data for \( \text{DCO} \) between our study and others may be related to our strict biopsy criteria for diagnosis of toxicity or to our inclusion of an amiodarone-treated group with pulmonary abnormalities unrelated to amiodarone.

Analysis of the BAL fluid cell counts revealed no single or combination of variables that were able to distinguish the toxic group from the other two amiodarone-treated groups. Further, the sensitivity, specificity, and predictive value of BAL fluid cell number or distribution were not diagnostically reliable.

Several groups have reported BAL fluid results in patients with amiodarone toxicity.\(^{13,17,21,28,29}\) Many of

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**Table 3—Bronchoalveolar Lavage Cell Counts**

<table>
<thead>
<tr>
<th></th>
<th>Control (n = 53)</th>
<th>Nontoxic (N = 13)</th>
<th>Toxic (n = 11)</th>
<th>Sick (N = 6)</th>
<th>ILD (n = 27)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total, cell/μl</td>
<td>105 ± 11</td>
<td>359 ± 95</td>
<td>441 ± 84</td>
<td>275 ± 126</td>
<td>790 ± 244</td>
</tr>
<tr>
<td>Macrophages, cell/μl</td>
<td>89 ± 10</td>
<td>322 ± 95</td>
<td>288 ± 69</td>
<td>95 ± 36</td>
<td>431 ± 135</td>
</tr>
<tr>
<td>Macrophages, %</td>
<td>5 ± 2</td>
<td>85 ± 4</td>
<td>66 ± 7</td>
<td>32 ± 6</td>
<td>210 ± 102</td>
</tr>
<tr>
<td>Lymphocytes, %</td>
<td>12 ± 1</td>
<td>12 ± 1</td>
<td>17 ± 5</td>
<td>17 ± 5</td>
<td>22 ± 4</td>
</tr>
<tr>
<td>Neutrophils, cell/μl</td>
<td>10 ± 1</td>
<td>10 ± 1</td>
<td>11 ± 4</td>
<td>79 ± 33</td>
<td>147 ± 129</td>
</tr>
<tr>
<td>Neutrophils, %</td>
<td>5 ± 2</td>
<td>5 ± 2</td>
<td>17 ± 7</td>
<td>24 ± 14</td>
<td>15 ± 4</td>
</tr>
<tr>
<td>Eosinophils, cell/μl</td>
<td>0.5 ± 0.2</td>
<td>1.3 ± 1</td>
<td>4.3 ± 2.0</td>
<td>0.3 ± 0.2</td>
<td>50 ± 31</td>
</tr>
<tr>
<td>Eosinophils, %</td>
<td>0.6 ± 0.2</td>
<td>0.2 ± 0</td>
<td>1.0 ± 0.5</td>
<td>0.3 ± 0.2</td>
<td>4.2 ± 1.6</td>
</tr>
</tbody>
</table>

*Values expressed as mean ± standard error. ILD = interstitial lung disease.

\( t_p < 0.05 \) vs control.

\( t_p < 0.05 \) vs nontoxic.
these reports lack control subjects.\textsuperscript{18,19,21} Others have only healthy volunteers as control subjects.\textsuperscript{30} Our study extends the published literature because both asymptomatic amiodarone-treated and healthy volunteers were used as control subjects. Further, two groups of diseased control subjects were also analyzed: the ILD group and the amiodarone-treated group examined for a pulmonary process unrelated to amiodarone. The inclusion of the two amiodarone-treated control groups is especially important because data derived from this comparison are relevant to the common clinical setting in which a physician must distinguish between amiodarone-induced interstitial pneumonitis, infectious pneumonia, congestive heart failure, and a number of other pulmonary disorders in the amiodarone-treated patient.

Several patterns of BAL fluid cell findings are reported to be associated with amiodarone toxicity. These include BAL fluid lymphocytosis, neutrophilia, eosinophilia, and normal BAL fluid differential cell counts. Of the studies that report a differential of BAL fluid cells or allow such conclusions to be drawn from the data presented, two studies found a normal differential of BAL cells.\textsuperscript{13,21} Three studies found 25 percent to 66 percent of patients with amiodarone-induced pneumonitis to have normal differential cell counts.\textsuperscript{17,18,20} The other patients with amiodarone-induced pneumonitis in these three studies had increased percentages of lymphocytes, neutrophils, or eosinophils. BAL fluid differential cell counts were abnormal in all patients with amiodarone-induced pneumonitis in only one study.\textsuperscript{40} In accordance with most of the cited reports, we found patients with amiodarone-induced pneumonitis to have either normal differential cell counts (3/11) or differential cell counts dominated by neutrophils (3/11), lymphocytes (4/11), or a mixed pattern (1/11). It has been speculated that amiodarone-induced pneumonitis may result from both direct drug-induced toxicity\textsuperscript{28,31} and a hypersensitivity injury.\textsuperscript{26,32-35} This dual toxic mechanism may account for the various differential cell count patterns observed. Differences in differential cell counts may be related to the small numbers sampled by each study.

None of the variables we measured was sufficiently sensitive or specific to reliably distinguish between amiodarone-treated volunteers, patients with amiodarone-induced pneumonitis, and patients treated with amiodarone examined for pulmonary abnormalities unrelated to amiodarone. BAL fluid analysis can complement lung biopsy specimens that yield nonspecific abnormalities in amiodarone-induced interstitial pneumonitis.\textsuperscript{30} BAL fluid culture and cytologic examination may narrow the differential diagnosis in suspected amiodarone-induced pneumonitis, but currently amiodarone-induced interstitial pneumonitis may be diagnosed only by exclusion of other pulmonary pathologic processes.

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26 Dunn M, Glassroth J. Pulmonary complications of amiodarone toxicity. Prog Cardiovas Dis 1989; 31:447-53

Recertification Examination in Critical Care Medicine

The American Board of Internal Medicine has announced the following:
Registration period
Examination dates
January 1, 1993-April 1, 1993
November 3, 1993
For information and application forms, contact the Registration Section, ABIM, 3524 Market Street, Philadelphia 19104 (800-441-2246).