Amiodarone Pulmonary Toxicity*  
Recognition and Pathogenesis (Part I)

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Amiodarone is an iodinated benzofuran derivative that represents a new and extremely effective therapy for certain life-threatening cardiac rhythm disturbances. There are numerous side effects associated with amiodarone therapy including corneal deposits in over 90 percent of the patients taking the drug, abnormal liver function tests, hyperthyroidism and hypothyroidism, bluish discoloration of the skin, bone marrow suppression, coagulopathies, peripheral neuropathies, and others. 1.4 Pulmonary toxicity, however, represents the most serious adverse reaction limiting the clinical efficacy of this new antidysrhythmic drug.

The incidence of side effects associated with amiodarone therapy ranges from 40 to 93 percent. 1,4,5,6 A recent review of the overall benefits and side effects states that the actuarial incidence of discontinuing the drug due to side effects is 52 percent at two years and 82 percent at four years. 4 This is especially important since Dean et al. 4 reported that 45 percent of patients die of an arrhythmia shortly after discontinuing amiodarone therapy. In addition to the abnormalities produced in other cells and tissues, amiodarone has an adverse effect on the metabolism of other drugs, particularly digitalis, warfarin, diphenylhydantoin, procaïnamide, quinidine, and others, requiring the lowering of doses of these drugs. 5,6 These lower doses must be maintained for one to three months or more after amiodarone therapy is discontinued because of the prolonged half-life of the drug. 7,8

The incidence of amiodarone pulmonary toxicity (APT) varies from 0 to 61 percent, 1,18 with an estimated mortality of 1 to 33 percent. 1,7,9,16-18,20 A reasonable estimate of the current incidence would be that 5 to 7 percent of patients receiving amiodarone will develop APT, and 5 to 10 percent of them will die of the adverse effect. Despite widespread use of amiodarone for nearly two decades in Western Europe, there were no reported cases of associated pulmonary toxicity until 1980, after the drug was introduced as an investigational agent in this country. 4 This may have been partly a result of the higher doses being used in this country for the more selective treatment of refractory life-threatening ventricular rhythm disturbances. Since the recognition of this serious adverse effect, amiodarone pulmonary toxicity has been diagnosed worldwide.

Currently, most patients receiving amiodarone therapy have serious underlying cardiomyopathy or coronary artery disease. It is difficult to evaluate nonspecific pulmonary symptoms and findings in this group of patients receiving amiodarone, because the differential diagnosis includes complications of the underlying disease: namely, congestive heart failure and pulmonary embolism. The clinician must utilize the most appropriate tools for each individual patient to best determine the cause for the apparent underlying lung disease. The need for “individualizing” diagnostic and therapeutic approaches for each patient cannot be overstated.

Clinical Presentation

In many cases, there appear to be two separate types of presentation of patients with APT, 16,18,22,23 which has been recognized by very few authors. One is the more common variety of an insidious onset of nonproductive cough, dyspnea, weight loss, and occasionally fever associated with parenchymal infiltrates, predominantly a diffuse interstitial pattern. The chest x-ray almost always correlates with the clinical symptoms, meaning that the symptoms usually do not precede the change in the chest roentgenogram. The insidious onset of this type of reaction rarely begins before two months on therapy, and rarely in a patient receiving less than 400 mg/day.

The second type of presentation is estimated to
occur in about one third of the patients and is associated with a more acute onset. The chest roentgenogram shows a predominant alveolar pattern with a patchy distribution not uncommonly involving the peripheral areas of the lung. This presentation is more typically associated with fever and may mimic an infectious pneumonia. However, the more acute symptoms may also suggest possibilities of pulmonary embolism or congestive heart failure. It is unclear whether the acute variety is more often fatal than the insidious variety, but an aggressive approach to the evaluation and management of these patients seems appropriate (see below).

Signs and symptoms of APT are unfortunately nonspecific. Cough is typically nonproductive. Pleuritic pain is common, but pleural effusion is unusual. Clearly, the major differential diagnosis of pleuritic pain in this patient population will include pulmonary embolism and an infectious pneumonia. Dyspnea is present in one half to three fourths and, of course, in all subjects when the disease progresses. Fever may be present in one third to one half of patients. Weakness and weight loss are also common and may suggest possible underlying infection or malignancy. Opportunistic pulmonary infections with mostly gram-negative organisms have been reported in a few series.5,84

Physical examination typically reveals bilateral rales. An occasional pleural rub may be heard, particularly if pleuritic pain is a presenting complaint. Clubbing has not been reported. Physical findings to determine the presence or absence of congestive heart failure are clearly important. However, to this point in the evaluation of the patient, little information is available to help confirm or deny the possible diagnosis of APT.

Peripheral Blood Findings

Patients with APT may have nonspecific elevation of the WBC count, lactate dehydrogenase (LDH) activity, and an elevated erythrocyte sedimentation rate (ESR). The elevated ESR is of particular interest, as it is present in 50 to 100 percent of subjects with APT,9,13,25,26,28 and, although not pathognomonic, it would not be expected in congestive failure or pulmonary embolism, the major differential diagnostic considerations in this setting. Eosinophilia has been reported in only a few cases;66 the antinuclear antibody (ANA) test; when reported, is either negative or of a low titer.

Amiodarone levels in the blood have been proposed as means to monitor possible toxicity.5,10 Normal therapeutic serum levels range from 1.0 to 3.5 µg/ml.5,10 Rotmensch et al39 reported arrhythmias recurred in 40 percent of patients with serum amiodarone concentrations of less than 1.0 µg/ml, whereas only 14 percent of the patients with higher concentra-

tions had recurrences. Unfortunately, there is no consistent evidence to indicate that peripheral blood levels of either amiodarone or its primary metabolite, desethylamiodarone, are predictive or diagnostic of amiodarone pulmonary toxicity. It is well recognized that amiodarone has an extremely long pharmacologic half-life (approximately 40 to 70 days, and serum and tissue levels of amiodarone can be measured long after discontinuing the therapy.6 It is possible that tissue levels of the drug more accurately reflect specific organ toxicity, but to our knowledge no studies to date have examined this finding in a prospective controlled study.

Serum levels of reverse T3, an inactive metabolite of T4, have also been proposed as a useful test to predict APT as well as its antidyssrhythmic effect.97 This remains controversial; however, the measurement of metabolic factors such as reverse T3 potentially offer a more direct monitor of the "physiologic" effect of amiodarone. To date, there are no serum markers that offer verifiable diagnostic or predictive information regarding APT.

Pulmonary Function

Pulmonary function testing reveals typical changes of restrictive lung disease in most cases of APT.15,28 The diffusing capacity for carbon monoxide (Dsb) is the physiologic test most frequently recommended to assess parenchymal involvement secondary to the drug. Some authors have included the finding of at least a 15 percent decrease in Dsb or total lung capacity in the definition of amiodarone pulmonary toxicity.15 However, pulmonary function testing is not without its limitations, as many patients with cardiomyopathy and congestive failure often have evidence of a mild decrease in lung volumes and Dsb, possibly secondary to interstitial lung edema. Furthermore, virtually all authors have incorporated physiologic parameters such as Dsb in their definition of APT, thus establishing a circular argument and making the interpretation and correlation of physiologic changes with APT very difficult. It has also been suggested that a decline in Dsb during therapy is not necessarily predictive of APT, since it can occur in patients receiving amiodarone without apparent clinical toxicity.16 Despite these limitations, baseline studies are useful and probably necessary in most patients receiving amiodarone to assist in the long-term assessment of possible parenchymal toxicity.

Roentgenographic Abnormalities

Chest x-rays represent the primary test for surveillance of patients for evidence of APT.9,13,14,16,18 Although most roentgenographic changes will be bilateral and diffuse, localized areas in the periphery of the lungs such as the apices may also be involved, not unlike
those seen in chronic eosinophilic pneumonia or apical tuberculosis.18,19 The roentgenographic changes range from those of a pure alveolar pattern (localized or diffuse) to a nearly pure interstitial pattern, with a combination of the two being most common. It is not uncommon for the pattern to be asymmetric. Hilar adenopathy does not occur, and pleural effusion is very uncommon.20 Clearly, the chest x-ray is not only a primary means to detect early evidence of amiodarone toxicity; it also represents an important screening parameter to assess evidence for cardiomegaly and cephalization of pulmonary blood flow secondary to congestive failure, a possibility which must frequently be considered seriously in the differential diagnoses of these patients. The clinician must be aware of the widely variable chest x-ray film appearances and consider the possibility of amiodarone pulmonary toxicity with any new or developing parenchymal or pleural abnormality.

Other Imaging Techniques

Both computerized tomography (CT) and radionuclide studies, such as gallium 67 lung scanning, have been proposed as useful monitors of APT.20-28 Without question, these scans can be sensitive detectors of parenchymal or pleural diseases, but their clinical utility is limited, since high-quality chest roentgenograms offer excellent evaluation of the parenchyma, cost less, and can often be compared with several prior films to determine whether significant changes have occurred.

The CT scan, however, does offer a unique ability to assess increases in lung density, which may occur with APT. Amiodarone, as noted earlier, is an iodinated compound, and thus its accumulation in tissue may be associated with an increase in tissue density, secondary to the accumulation of iodide.23,24 The clinical difficulties with the use of CT scan in the evaluation of individual patients may arise when attempting to determine whether a specific change in lung density represents toxicity or simply reflects the normal accumulation of amiodarone in lung tissue, secondary to the therapeutic effect of the drug.

Gallium scanning of the lung has been utilized as a monitor for the presence of activated inflammatory or immune effector cells in the lungs.25 Since APT may be associated with an inflammatory or immune response in some cases, it is reasonable to suggest that this investigative approach may help in assessing parenchymal changes secondary to use of the drug.20,22,23,26-28 Gallium scans may be especially useful in helping to distinguish the interstitial edema of congestive failure from the inflammatory or immune response associated with APT.28 However, there is a case report of a negative gallium scan in a patient with APT.28 Difficulties that might also be associated with the routine use of gallium scanning include its relatively high costs, high radiation dose, prolonged testing interval of 48 to 72 hours, and, in most centers, the inability to quantify the gallium uptake (limiting utility of comparing scans).

It is important, however, to continue to assess imaging techniques such as CT scans and gallium scans, which offer alternative methods to routine chest films in the non invasive assessment of APT. Prospective studies should be conducted to evaluate large series of patients receiving the drug to determine whether these newer modalities offer useful information and can distinguish toxic changes secondary to amiodarone use from the nontoxic changes attributable to simple drug effect alone.

Bronchoscopic Findings

Most progressive lung parenchymal disorders (regardless of etiology) will eventually be evaluated by flexible fiberoptic bronchosco pic examination. If a symptomatic patient receiving amiodarone does not have clear-cut evidence of APT by history, examination, and routine noninvasive studies, and amiodarone is the best available therapy, bronchoscopic evaluation is often undertaken to support the diagnosis of APT and to help exclude other diagnostic possibilities, such as infection or malignancy.

Transbronchoscopic lung biopsy (despite the small sample size) often reveals typical changes described with amiodarone toxicity, including the presence of characteristic cytoplasmic inclusions in the cells, giving them a "foamy" appearance (Fig 1a).10,12,13,16-18,23,25,36,37 Ultrastructurally, these inclusions are associated with lamellar body formation suggestive of phospholipid accumulation. Although the "foamy" changes have been characteristically described in patients with toxicity, they may also be seen in patients without evidence of toxicity.16-18,33 Dake et al28 described these lysosomal inclusion bodies in liver cells, lymph nodes, WBCs, and the lung cells. Stein et al28 also found typical cytoplasmic lamellar inclusions in foamy macrophages in pleural effusions. Thus, although this finding is relatively characteristic for drug effect secondary to amiodarone, it is not specific for the toxicity associated with the drug. However, the absence of foamy inclusions would make the diagnosis of APT unlikely.

Lung biopsy specimens (either transbronchoscopic or open) often reveal parenchymal changes consistent with a mild nonspecific interstitial pneumonitis (PMNs, lymphocytes, etc) but occasionally can reveal severe changes consistent with diffuse alveolar damage.29 In the absence of another explanation, these findings are consistent with (although not diagnostic of) APT, provided lipid-filled inclusions are also present. Dean et al30 found intra-alveolar hemorrhage in...
patients with amiodarone pulmonary toxicity. This study indicated that the phospholipid content as well as specific phospholipids within the cells were markedly increased in patients with amiodarone toxicity. Methods that quantitatively assess specific biochemical parameters may offer a more specific tool to discriminate between drug effect and drug toxicity.

Some patients with amiodarone pulmonary toxicity also have evidence of an inflammatory or immune response in the lung by bronchoalveolar lavage. Increase in both polymorphonuclear leukocytes (PMNs) and T-suppressor/cytotoxic lymphocytes (CD8+) have been described in patients with toxicity. These findings are also compatible with hypersensitivity reactions associated with organic antigen exposure and other types of drug-induced lung disease such as that associated with gold or nitrofurantoin. In our series, approximately one third of our patients with APT have normal cell differential counts on BAL with the remaining subjects having either a marked increase in CD8+ lymphocytes or PMNs or both. When present, the findings of increased numbers of T-suppressor/cytotoxic lymphocytes with or without PMNs strongly support the diagnosis of amiodarone toxicity; when absent (cell differential is normal), the findings from bronchoalveolar lavage neither support nor exclude the diagnosis.

**RISK FACTORS FOR TOXICITY**

There are several reports suggesting that preexisting lung disease—ie, abnormal chest roentgenogram findings and/or pulmonary function status prior to the initiation of therapy—predisposes to APT. Kudenchuk et al prospectively studied 69 patients before and during amiodarone therapy and found that 28 percent with a pretreatment Dsb of less than 80

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**Figure 1.** Lung specimens from subject with amiodarone pulmonary toxicity. A, Transbronchoscopic lung biopsy revealing typical foamy inclusions (H&E stain, ×640). B, Bronchoalveolar lavage cytopreparation smear with normal cell differential and marked foamy appearance of alveolar macrophages (Diff-Quick stain, original magnification ×640).

six of their 11 patients with APT.

Bronchoalveolar lavage has potential as an important adjunctive test in the evaluation of suspected APT. Lavage provides excellent cellular material for morphologic assessment of "foamy" inclusions in alveolar macrophages (Fig 1b) and permits the easy sampling of inflammatory and immune effector cells within the lower respiratory tract (Fig 2). As noted previously in the discussion of biopsy specimens, the presence of "foamy" macrophages or lung cells can also be detected in up to one half nontoxic patients receiving amiodarone. Thus, the simple morphologic detection of "foamy" cells by bronchoalveolar lavage will not be diagnostic of toxicity.

If the amiodarone-induced pulmonary "phospholipidosis" is related to the development of toxicity, alternative methods are required to test this hypothesis. Recently, direct quantitative determination of phospholipid content and a profile of alveolar macrophages were obtained from the bronchoalveolar lavage of

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**Figure 2.** Bronchoalveolar lavage cytopreparation smear from subject with amiodarone pulmonary toxicity revealing marked increase in percentage of lymphocytes and polymorphonuclear leukocytes. Typically, lymphocytes are predominantly CD8 positive reflecting a reversal of the helper/ suppressor ratio, a finding previously associated with hypersensitivity reactions (Diff-Quick stain, original magnification ×640).
percent predicted eventually showed changes consistent with APT compared to only 5 percent if the pretreatment Dsb was normal. Similarly, among patients with an abnormal pretreatment chest x-ray film findings, 40 percent had an increase in infiltrates. The authors concluded that an abnormal pretreatment chest roentgenogram and Dsb increased the risk of APT by nearly tenfold, suggesting that patients with initial abnormalities in these parameters should be considered for alternative therapy. The package insert that accompanies the drug also emphasizes precaution. Dean et al. studied 171 patients with 6.4 percent (11 patients) developing APT. Of interest, six of the 11 subjects (55 percent) who developed toxicity had preexisting lung diseases compared with only 10/160 (6.25 percent) who remained free of clinical toxicity. Thus, preexisting lung disease appears to increase the risk of clinically evident toxicity in patients receiving amiodarone. It is also possible that preexisting lung disease does not actually increase the true risk of toxicity; rather, the development of drug toxicity is much easier to detect in individuals who already have limited pulmonary reserve. In either case, the benefit-risk ratio of amiodarone therapy must be carefully evaluated in patients with underlying lung disease. The risk of developing APT may also be related to the dose of the drug and duration of therapy, with only a few cases occurring in individuals receiving less than 400 mg/day. In one report, however, 31 percent of the patients received less than 400 mg/day. The total cumulative amount of amiodarone (rather than the daily dose) may be an important factor in assessment of risk for APT. For example, patients receiving as little as 200 mg daily may develop APT after several years of therapy. On the other hand, there are reports of patients having received as much as 900 g of amiodarone as a total cumulative dose before there was any evidence of clinical pulmonary toxicity. The overall assessment of risk for APT may be increased with higher daily and cumulative doses. However, the assessment of toxicity risk for any specific individual must be tempered by the knowledge that many other still unrecognized factors may be operative.

METHOD OF DIAGNOSIS

There are no laboratory or clinical data currently available that alone unequivocally establish the diagnosis of APT. To make a "clinical" diagnosis of APT requires the exclusion of other diagnostic possibilities (especially occult congestive heart failure) together with a reasonable constellation of symptoms or findings consistent with the diagnosis. Kudenchuk et al. defined APT as any two of the following findings: (1) new or worsening symptoms; (2) new abnormalities on, or worsening of chest roentgenograms; or (3) a decline of at least 15 percent in the Dsb or total lung capacity. Several additional factors should be considered in the establishment of a "clinical" diagnosis of APT: (1) the absence of phospholipidosis in lung cells makes the diagnosis unlikely; (2) a marked CD8+ lymphocytosis in the lavage is strongly supportive; (3) lung biopsy material that reveals diffuse alveolar damage, interstitial pneumonitis, or fibrosis is consistent with APT; and (4) drug withdrawal with or without steroid therapy should in most cases reverse some or all of the abnormalities in APT. Depending on how extensive an evaluation is made of each individual patient (see below), some or all of the above factors should be incorporated into establishing the clinical diagnosis of APT.

The clinician must use all available information and resources to support the presence or absence of toxicity in each patient. In some cases (where alternative antidysrhythmic therapy is available), the amount of data necessary to support a "clinical diagnosis" of toxicity may be as little as that obtained from history, examination, chest x-ray film, and pulmonary function test results. However, when amiodarone represents the only or best available therapy to the patient, more extensive evaluation may be necessary prior to any consideration of its discontinuation. Clearly, the clinician must decide how far to pursue the diagnostic evaluation, based on not only the severity of presenting symptoms and findings, but also the necessity for amiodarone therapy and the possible risk associated with its withdrawal.

We think that using amiodarone under current FDA guidelines for treatment of "life-threatening ventricular arrhythmias refractory to other drugs," and with an incidence of adverse pulmonary reactions in 5 to 10 percent of treated subjects, a systematic approach to the evaluation of patients is necessary (Fig 3). Baseline data prior to the initiation of amiodarone therapy would become particularly useful should new symptoms or findings develop while the patient is receiving the drug. For example, failure to have baseline pulmonary function tests with Dsb limits the value of subsequent physiologic testing in the symptomatic patient. Which tests should be used for "surveillance" of toxicity in this patient population is unclear; as a practical matter, we recommend a history and chest x-ray examination every three months.

If a patient should develop new symptoms or chest x-ray findings suspicious for APT, we would simply repeat the baseline data evaluations. The major diagnostic decisions at this point relate to the confidence with which the clinician can exclude other diagnostic possibilities. If there may be respiratory infection or malignancy, early evaluation with bronchoscopic study and possibly open lung biopsy may be necessary. On the other hand, if congestive heart failure or pulmonary

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emboli are reasonable possibilities, further evaluation with echocardiography, ventilation-perfusion lung scanning, pulmonary arterial and wedge pressure determinations, and pulmonary angiography may be required. Pulmonary angiography may be necessary to rule out the diagnosis of pulmonary embolism, despite the report of a possibly increased risk of this procedure in patients with amiodarone toxicity.** The appropriateness of how aggressive to be in the diagnostic evaluation of an individual patient relates solely to the relative risk that a given patient may have an alternative diagnosis. Clearly, it is also possible that the patient may have more than one diagnosis.

The need to pursue further supportive evidence for the presence or absence of APT relates in part to the severity of presenting symptoms and signs, but more importantly to the availability of acceptable alternative antidysrhythmic therapy. For example, if a patient is receiving amiodarone for a relatively benign rhythm disturbance and evidence of mild parenchymal lung disease develops, the best diagnostic (and therapeutic) option is simply to discontinue amiodarone therapy. Frequently, within days or weeks the patient will have complete resolution of all pulmonary findings, and the clinical diagnosis of a "probable" APT will have been established.

In contrast, in the patient who requires amiodarone for a life-threatening rhythm disturbance as the best available therapy, the need for further supportive evidence of APT is appropriate. Although some centers use gallium lung scanning or CT of the chest to assist in the assessment of APT, we think that the clinical utility of these tests at this time is limited in the routine diagnosis of most patients. The next appropriate step in evaluation is usually bronchoscopic examination, with transbronchoscopic lung biopsy and bronchoalveolar lavage. Both procedures can help to exclude the presence of malignancy or respiratory infections and provide useful information in support of amiodarone pulmonary toxicity. Transbronchoscopic lung biopsy (despite the small sample size) may provide adequate tissue to help verify the extent of diffuse alveolar damage; bronchoalveolar lavage may detect the presence of T-suppressor/cytotoxic lymphocytes with or without PMNs supporting the diagnosis of hypersensitivity pneumonitis (if present). The morphologic finding of "foamy" macrophages and lung cells is not diagnostic of APT; however, its presence

*FIGURE 3. Proposed evaluation of patients receiving amiodarone. *APT = amiodarone pulmonary toxicity, PFTs = pulmonary function tests, Dx = diagnosis, CHF = congestive heart failure, PE = pulmonary emboli, DC = discontinue, TBLBX = transbronchoscopic lung biopsy, BAL = bronchoalveolar lavage, OLBX = open lung biopsy. **If amiodarone is necessary for life-threatening rhythm disturbance, consider rechallenge with lower dose of the drug.
certainly confirms significant drug effect, and if the biochemical determinations of phospholipid content of lung cells proves useful, this may represent a future diagnostic tool.38

Open lung biopsy has a limited role in the evaluation of patients with APT. In 24 cases of pulmonary toxicity at our institution, we have not needed to pursue an open lung biopsy to help establish the diagnosis or to exclude other important diagnostic possibilities. This is not to say that in some cases the choice to pursue open lung biopsy is not indicated, only that careful, complete evaluation with available diagnostic tools would likely preclude the need for open lung biopsy specimens in most cases.

**THERAPEUTIC OPTIONS**

Once the clinical diagnosis of APT has been made, a limited number of therapeutic options are available to the clinician. First, the most frequently used option is simply to discontinue amiodarone. In most cases, symptoms and findings will begin to resolve within a few days, although near-complete resolution may require several months. In general, the more insidious the onset of the disease, the slower the resolution. Clearly, the unusual occurrence of progressive pulmonary toxicity is possible despite discontinuation of amiodarone; this has been attributed to the long elimination half-life of the drug10 and its propensity to concentrate in target tissues such as the lung.29 Progression of pulmonary symptoms or findings, however, should alert the clinician to the possibility that other pulmonary diagnoses may be present; perhaps amiodarone toxicity is not the primary problem.

As with all drug-induced lung disease, the value of corticosteroid therapy is uncertain and substantiated only by anecdotal reports.12-14,16,19,30,46 In general, we use corticosteroids for amiodarone pulmonary toxicity when presenting symptoms or findings are severe and we hope to speed recovery of normal gas exchange. Typically, prednisone would be used at 40 to 60 mg daily with a tapering of the dosage over a subsequent two- to six-month period. Withdrawal of steroids too early has induced a recurrence in some patients.29 Corticosteroids also can be helpful when it is important to know as soon as possible whether the parenchymal lung disease is responding favorably to drug withdrawal. It is likely that corticosteroids facilitate resolution of pulmonary toxicity; what remains unknown, however, is whether the ultimate recovery is in any way modulated by corticosteroid intervention. As a practical matter, is is probably best simply to withdraw amiodarone therapy in most cases of suspected toxicity and observe whether this results in improvement. However, the judicious use of corticosteroids is very reasonable and should be strongly considered for patients with evidence for severe toxicity (eg, diffuse parenchymal involvement with pulmonary function test evidence of restrictive lung disease and loss of diffusing capacity).

It is also important to keep in mind that as symptoms or signs of APT resolve, the antidysrhythmic efficacy will also begin to dissipate. Typically, during the first few weeks following amiodarone withdrawal, the underlying rhythm disturbance can reappear.4 Close observation is required during this period to be certain the alternative therapy is equally efficacious in the control of the dysrhythmia.

Finally, one can use an option in the treatment of APT that is not usually considered for most types of drug-induced lung disease. When amiodarone may be the best or only therapy available, one can consider simply lowering the dose of amiodarone. For example, if a patient is receiving amiodarone, 400 mg daily (a typical maintenance regimen for the control of ventricular dysrythmias), and develops evidence of APT, the therapy can be discontinued for a few days and reinstated at a lower dosage; ie, 200 mg/day. In most cases, it is probably best to use corticosteroid therapy to help in the resolution of the pulmonary toxicity. It is possible to maintain patients on this lower dosage regimen of amiodarone, and corticosteroids may be needed for only a brief time (eg, weeks) or may be required long-term (as long as the patients receive amiodarone46). As with all corticosteroid regimens, the goal should be to use corticosteroids at the lowest possible efficacious dose. Surprisingly, this regimen has resulted in effective control of serious rhythm disturbances as well as control of the associated pulmonary toxicity.

**SUMMARY**

Amiodarone represents an important new approach in the treatment of serious cardiac rhythm disturbances and is associated with significant pulmonary toxicity in approximately 5 to 10 percent of patients. The recognition of APT in patients receiving the drug early in the course of the disease will likely preclude the development of a permanent loss of pulmonary function in these patients. It is important for the clinician to individualize both the diagnostic and therapeutic approach to the patient receiving amiodarone who is thought to have pulmonary toxicity secondary to the drug. Several diagnostic and therapeutic decisions are available, and it is important to constantly reevaluate the risk-benefit ratios of the decision making process. Future studies may improve insight into the assessment of APT and may permit the clinician to diagnose this toxicity at an earlier and potentially more reversible stage of the disease process.

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