SPECIAL ARTICLE

Practical Guidelines for Clinicians Who Treat Patients With Amiodarone

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Amiodarone has become an important drug for the treatment of supraventricular and ventricular arrhythmias, in short-term inpatient and outpatient settings. It may also have a role in affecting outcome in patients at high risk for arrhythmic events and sudden death; its place among available therapies is being established in clinical trials.

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Patterns of use of amiodarone are not uniform, either in academic or in community settings; overuse and underuse are likely real phenomena, although data are sparse and largely anecdotal. Guidelines for physicians who use amiodarone are unavailable. Because of the potential for serious toxicity with its use, knowledge of drug dosing, beneficial effects, and adverse effects is essential for proper patient management. This guideline was created as an approach to the use of amiodarone in clinical practice. The guideline reviews the indications for use of amiodarone and methods of initiation of therapy, suggests strategies for the follow-up of patients receiving amiodarone, and outlines the adverse effects of therapy.

The recommendations contained herein are based on the best available data or, where these are lacking, the collective experience of the members of the writing committee.

INDICATIONS FOR USE

Oral Amiodarone

Oral amiodarone is approved by the Food and Drug Administration for the treatment of life-threatening recurrent ventricular arrhythmias, such as ventricular fibrillation (VF) or ventricular tachycardia (VT) with hemodynamic instability.

This indication includes the stipulation that the arrhythmias are not responsive to other available antiarrhythmic agents or that the patients are intolerant of them.

It is the consensus of this committee that amiodarone should be used as the antiarrhythmic agent of choice, in connection with other therapies (eg, β blockers), in patients with sustained ventricular tachyarrhythmias who have structural heart disease, especially left ventricular dysfunction, and who are not candidates for an implantable cardioverter-defibrillator (ICD). This recommendation is based on the following: (1) 2-year efficacy rates in reducing arrhythmic events by more than 60%; (2) minimal negative inotropic effects and a low incidence of associated proarrhythmia; (3) long-term safety in patients after experiencing a myocardial infarction (as demonstrated in the European Myocardial Infarct Amiodarone Trial [EMIAT][1] and the Canadian Amiodarone Myocardial Infarction Arrhythmia Trial [CAMIAT][2]) and in patients with significant left ventricular dysfunction (as shown in the Grupo de Estudio de la Sobrevida en la Insuficiencia Cardiaca en Argentina trial [GESICA][3] and the Survival Trial of Antiarrhythmic Therapy in Congestive Heart Failure [CHF-STAT][4]); and (4) efficacy rates for empirical use of amiodarone, which are superior to electrophysiologically guided therapy with

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class 1 antiarrhythmic agents (shown in the Cardiac Arrest in Seattle: Conventional vs Amiodarone Drug Evaluation [CASCADE] trial[5]).

Several prospective trials (Antiarrhythmics Versus Implantable Defibrillators [AVID],[6] Cardiac Arrest Study Hamburg [CASH],[7] and Canadian Implantable Defibrillator Study [CIDS][8]) have demonstrated that an ICD is superior to empirical amiodarone therapy in preventing sudden cardiac death. Moreover, the AVID trial[6] showed improvement in overall survival. Of patients who have ICDs, 30% to 70% require concomitant antiarrhythmic treatment. Amiodarone is effective in slowing the rate of VT, as tested in the electrophysiology laboratory; this effect appears to be predictive of a better outcome. Although amiodarone can increase the defibrillation threshold, necessitating ICD retesting once the drug has been initiated, it may be useful for patients refractory to, or who are not candidates for, sotalol hydrochloride or other β-blocker therapy. In cases of extremely elderly or critically ill patients in whom an ICD might not be appropriate, amiodarone should be used as first-line therapy in hemodynamically unstable sustained VT. The role of electrophysiologic testing in patients receiving amiodarone is controversial, and remains to be clarified.

Although patients with nonsustained VT and left ventricular dysfunction are recognized to be at increased risk for sudden cardiac death, treatment of these arrhythmias is controversial. In the CHF-STAT[4] and the GESICA trial,[3] use of amiodarone had neutral overall effects on mortality in patients with ischemic cardiomyopathy and improved survival in those with nonischemic cardiomyopathy. Based on these studies, the consensus of this committee is that it is reasonable to use amiodarone in patients with significant left ventricular dysfunction and nonsustained VT that is symptomatic or concerning enough to warrant treatment.

Although not Food and Drug Administration–approved for use in atrial fibrillation, oral amiodarone is effective in controlling ventricular rate in atrial fibrillation and in maintaining sinus rhythm in more than 60% of patients during a 2- to 3-year period. Given its safety profile, especially in patients after a myocardial infarction and in patients with heart failure, amiodarone should be considered to be one of the drugs of choice in maintaining sinus rhythm in patients with paroxysmal atrial fibrillation. In patients without structural heart disease, amiodarone should be used if their atrial fibrillation is refractory to other agents or if the patient is intolerant of them.

Although preoperative oral amiodarone loading has been reported to significantly reduce the incidence of atrial fibrillation after aortocoronary bypass surgery,[9] this management strategy has not been widely accepted because of the widespread use of β blockers, logistical preoperative loading dose issues, and cost.

Intravenous (IV) Amiodarone

Intravenous amiodarone has been approved by the Food and Drug Administration for the treatment and prophylaxis of recurrent VF and hemodynamically unstable VT in patients refractory to other therapy. This indication is supported by 2 prospective, randomized, parallel, dose-response studies[10,11] that demonstrated a favorable trend toward a decrease in VT or VF events per hour and time to the first VT or VF event. Significantly fewer supplemental infusions were required in patients receiving IV amiodarone, 1000 mg/d, compared with those receiving smaller doses.

Intravenous amiodarone was reported to have comparable efficacy to IV bretylium tosylate in one study[11]; the mortality rate was not affected. Intravenous amiodarone is also approved to treat patients with VT or VF who are candidates for oral amiodarone but are transiently unable to take the oral preparation.

In critically ill patients who develop atrial fibrillation with rapid ventricular response, IV amiodarone has been found to be effective in controlling the ventricular rate through its short-term calcium channel-blocking and sympatholytic effects, although it is not approved by the Food and Drug Administration for this use. However, since acutely administered IV amiodarone has little effect on atrial refractory periods, placebo-controlled trials[12] have demonstrated no increase in efficacy in converting atrial fibrillation to sinus rhythm. One recent study suggests that IV amiodarone may minimize the occurrence of atrial fibrillation in patients who have undergone an aortocoronary bypass.[13] Further trials should verify these findings before routine prophylactic use of amiodarone can be recommended.

DRUG DOSING

Amiodarone appears to have an unparalleled efficacy, a broad spectrum of antiarrhythmic action, and a complex array of adverse effects when used as an antiarrhythmic and antifibrillatory compound. Some knowledge of its pharmacodynamics, electropharmacologic features, and pharmacokinetics is essential as a basis for initiating therapy in the hospital or in the outpatient setting and for its safe and effective use during long-term therapy.

The complexity of the electropharmacologic profile of amiodarone is striking.[14] The drug lengthens repolarization, but it is not just another class 3 antiarrhythmic agent; it exhibits all 4 electrophysiologic classes of action. Its sodium channel–blocking action is seen largely at rapid heart rates but is not associated with the proarrhythmic effect typical of class 1 agents. Unlike the class 1 drugs, it neither increases mortality nor depresses ventricular function; in fact, it increases left ventricular ejection fraction in patients with heart failure. Its class 2 or antiadrenergic actions resemble those of β blockers but without their adverse effects, in part because its β-blocking activity is relatively weak. It differs from all other class 3 agents in (1) rarely producing torsade de pointes despite markedly lengthening the QT interval and (2) maintaining its efficacy at rapid heart rates. The compound can be administered "empirically," without electrophysiologic testing or Holter-guided evaluation, which simplifies its use in clinical practice.[15]

Amiodarone is highly lipophilic, with a long elimination half-life that is highly variable among patients (35-110 days). It may require months for blood levels to reach steady state, and levels are not correlated with clinical effects. Thus, caution must be used in assessing generic versions of the compound exclusively based on drug bioequivalence. The oral bioavailability of amiodarone averages 30% to 50%, and excretion via the kidneys is minimal; it can, therefore, be administered safely in anephric patients. The amiodarone dose does not need to be reduced in patients with renal disease; the drug and its metabolite are not dialyzable. Amiodarone is metabolized in the liver, its major metabolite being desethylamiodarone, which is pharmacologically active and has a longer elimination half-life than that of the parent compound. Because they are lipophilic, amiodarone and its metabolites are extensively accumulated in the liver, lung, fat, skin, and other tissues. The onset of action after IV drug administration occurs within several hours, whereas after oral administration the onset of action may require 2 to 3 days, depending on the dosing regimen. There is a reasonable linearity between plasma drug concentration and dose of amiodarone, and the plasma level of the drug in patients successfully treated with amiodarone usually ranges between 1.5 and 2.5 μg/mL; desethylamiodarone levels also increase as a function of time and reach a level either comparable to or in excess of that of the parent compound. However, there is a poor correlation between plasma levels and either the therapeutic or toxic effects of the drug. As a result, established pharmacokinetic principles may not provide a reliable basis for predicting the attainment of steady-state therapeutic effects of the drug.

There are few absolute contraindications to the use of amiodarone. The drug is best avoided in patients with active thyrotoxicosis, cirrhosis of the liver or other forms of advanced liver disease, and severe pulmonary disease (especially extensive fibrosis) and in patients with a history of major adverse effects due to previous exposure to the drug.

Oral Drug Initiation

Clinical experience with amiodarone has led to various drug-dosing considerations that are of practical importance, whether the drug is being used to maintain sinus rhythm in paroxysmal atrial flutter and fibrillation, to treat ventricular arrhythmias as a principal mode of therapy, or as adjunctive therapy in patients with ICDs. The most significant principle of therapy is to use the lowest dose of the drug that will produce the desired therapeutic effects to reduce the risk of intolerable or potentially serious adverse effects. Although high-dose loading regimens have been used, advantages over lower-dose loading regimens have not been demonstrated,[16] although they may be well tolerated.[17] The relative merits of IV loading in place of these high-dose oral regimens is unknown.

An initial loading dosage, in patients with ventricular arrhythmias, of 800 to 1600 mg/d (usually in divided doses) for up to 2 to 3 weeks is reasonable. At this stage, the dose may be reduced to 400 to 600 mg/d, since such a regimen is usually adequate to produce close to a steady state in patients with ventricular arrhythmias. For many patients, this dose will be sufficient for long-term maintenance during the first year. In some patients, the dose may be reduced even further (to 200-300 mg/d). Dose reduction may be necessary earlier in the event of adverse effects, especially constipation and central nervous system symptoms. Lower loading and maintenance doses are preferable in women and in all patients with a low body weight.[18] Reducing the dose to 200 mg/d in patients being treated for ventricular arrhythmias may result in a high risk of arrhythmia recurrence, especially as a function of time. In such situations, the addition of a second antiarrhythmic drug, in particular a β blocker, may be helpful. Alternatively, an ICD may be implanted if an increase in amiodarone dose is deemed undesirable or is not well tolerated. Lower doses of amiodarone in conjunction with an ICD can minimize the risks of arrhythmia recurrence and adverse drug effects, while the ICD offers protection against arrhythmic death. For the initial control of VT and fibrillation, therapy is always initiated in the hospital except in patients who already have an ICD, in whom amiodarone therapy can be initiated on an outpatient basis.

In the management of patients with atrial fibrillation, loading and maintenance doses can be much lower than those for life-threatening ventricular arrhythmias and therapy can be initiated safely in the outpatient clinic. Caution must be exercised in patients in whom there is a suspicion of sinus or AV node dysfunction, in whom drug-induced bradycardia may develop. Various regimens have been recommended. A reasonable loading dosage is 600 to 800 mg/d (in 2 divided doses) for 2 to 4 weeks; thereafter, the dose can be reduced to 400 mg/d, and further reduced to 100 to 300 mg/d at 3 to 6 months, depending on clinical efficacy and the development of adverse effects. The usual maintenance dose for atrial fibrillation is 200 mg/d, although in the event of breakthrough arrhythmias, short periods of higher doses may be required; higher maintenance doses may be required in some patients. In some situations, satisfactory clinical efficacy can be obtained with amiodarone, 200 mg/d, given 5 days a week, especially in women with a low body mass index. During loading and maintenance dosing, drug interactions with digoxin and warfarin sodium must be recognized, since these drug dosages will have to be reduced accordingly.

IV Dosing

There appears to be substantial individual variation in response time during the initiation of IV amiodarone therapy.[19] Consequently, dosing recommendations are derived from clinical trial experience and provide guidelines only; close patient observation and dose adjustments are essential for optimum benefit without adverse effects. For example, hypotension and other adverse cardiac effects that may be seen

during initial rapid infusion may improve significantly with a decrease in the rate of infusion.[20-22] In contrast, supplemental IV boluses are frequently needed for patients with recurrent arrhythmias during the early phases of dosing. The recommended initial IV loading dose[10,22] is 150 mg administered for 10 minutes, followed by an intermediate infusion of 1 mg/min for 6 hours and 0.5 mg/min thereafter. Supplemental boluses of 150 mg may be given for 10 to 30 minutes for recurrent arrhythmias, but because hypotension occurs more frequently at daily doses greater than 2000 mg, no more than 6 to 8 supplemental boluses in any 24-hour period may be possible. Plasma drug levels are not routinely used because they are high and uninterpretable in the early phases of therapy and because there is a wide variation in "effective concentrations" of parent compound and metabolite. When given intravenously, amiodarone should be mixed in a 5% dextrose solution and should be infused with a volumetric pump. If used in high concentrations (>2 mg/mL), it must be delivered through a central vein because it can cause peripheral phlebitis (in <3% of patients). Amiodarone does not need light protection but is physically incompatible with several drugs, such as heparin, with which it is frequently used. In multicenter trials, the median duration of IV amiodarone therapy was 4 days, but there was wide variation. Patients who could not take oral medication were treated for 3 to 6 weeks without difficulty.

Transition to Oral Therapy

The bioavailability of oral vs IV amiodarone varies from 30% to 70%. Bioavailability appears to be lower in elderly patients and in those with cardiopulmonary disease. Recommendations regarding the transition from IV to oral therapy take into account these properties, in addition to the fact that there may be a delay of 4 to 5 hours between ingestion of the oral drug and an increase in the plasma level. Generally, the longer the patient has been receiving IV therapy, the less the need for the customary large oral loading doses.

More than 90% of the patients who received IV amiodarone in controlled clinical trials eventually underwent oral therapy, principally because they had significant arrhythmias that were not due to an easily reversible cause. When the drug is used in clinical situations in which the underlying condition can be remedied, such as in patients with an acute myocardial infarction who have undergone successful revascularization, the rate of conversion to oral therapy will probably decline. Patients who have been receiving IV therapy for more than 2 to 3 weeks can be started safely on maintenance doses of oral amiodarone (300-400 mg/d). Those treated for 1 week or less should probably receive the usual oral loading regimen of 800 to 1200 mg/d, whereas an intermediate dose of 400 to 800 mg/d might be suitable for patients who fall in between these time frames. If there is concern about gastrointestinal tract function, both oral and IV therapy should be maintained for a few days. These recommendations are empirical, based on the usual target total drug dose for in-hospital drug loading, and are not based on careful pharmacological trials.

Occasionally, a patient who is receiving long-term therapy temporarily cannot take oral medication. Because amiodarone is slowly eliminated from the body, cessation of therapy for a few days is of little consequence, but patients should have electrocardiographic monitoring within 5 to 7 days because of the drug's biphasic elimination profile. If oral therapy cannot be started after that time, or if there is doubt about adequate gastrointestinal tract absorption, IV therapy can be substituted. A loading dose is not necessary; based on the known range of its bioavailability, infusion of 30% to 70% of the daily oral dose will suffice.

Intravenous amiodarone has been used for the treatment of patients who have received long-term oral therapy but who have recurrent arrhythmias. Under these circumstances, it should be assumed that the patient has insufficient myocardial tissue drug concentrations, especially if the QT interval is not prolonged. It is customary in these situations to use the recommended loading and maintenance doses of the IV formulation until the arrhythmia is suppressed, and then to prescribe oral therapy.

Assessment of Efficacy

After a patient has received loading doses of either oral or IV amiodarone, the question may arise as to the need for an evaluation to confirm clinical efficacy before hospital discharge. Arrhythmia suppression with an IV antiarrhythmic drug does not necessarily predict the efficacy of its oral formulation. Moreover, the sporadic nature of recurrent VT or VF and paroxysmal atrial arrhythmias can make short-term suppression of arrhythmia difficult to interpret vis-à-vis long-term suppression. Options include either monitoring to determine whether, for example, repetitive forms, especially nonsustained VT, have been suppressed or performing electrophysiologic testing. There are no definitive data to prove the value of either method. Patients with paroxysmal atrial arrhythmias need not undergo such testing.

FOLLOW-UP

Appropriate long-term management of patients taking amiodarone is essential. Without proper assessment of the patient by the physician, the risk-benefit ratio of using amiodarone may weigh in favor of risk rather than benefit. Adverse effects are common, with a prevalence as high as 15% in the first year of use and up to 50% during long-term use (**Table 1**),[20-22] indicating a cumulative adverse effect profile. Fortunately, many of these adverse effects are manageable and the need to stop amiodarone therapy due to serious adverse reactions is relatively low, occurring in less than 20% of patients. Specific evaluation for adverse effects appears to identify the development and prevent the progression of serious adverse effects. Accelerated follow-up is required when there is development of an adverse effect. Optimizing therapy with amiodarone entails using the lowest effective dose to minimize adverse effects.

Table 1. Adverse Reactions to Amiodarone

Reaction	Incidence, %	Diagnosis*	Management
Pulmonary	1-20	Cough, especially with local or diffuse infiltrates on chest x-ray film, suggesting interstitial pneumonitis; and decrease in D_LCO from baseline	Usually discontinue drug; corticosteroids may be considered; occasionally, can continue drug if levels high and abnormalities resolve; rarely, continue amiodarone with corticosteroid if no other option
Gastrointestinal tract	30	Nausea, anorexia, and constipation	Symptoms may decrease with decrease in dose
	15-50	AST or ALT level greater than 2 times normal	If hepatitis considered, exclude other causes
	<3	Hepatitis and cirrhosis	Consider discontinuation, biopsy, or both to determine whether cirrhosis is present
Thyroid	1-22	Hypothyroidism	Thyroxine
	<3	Hyperthyroidism	Corticosteroids, propylthiouracil or methimazole, and may need thyroidectomy
Skin	<10	Blue discoloration	Reassurance and sunblock
	25-75	Photosensitivity	Sunblock
Central nervous system	3-30	Ataxia, paresthesias, peripheral polyneuropathy, sleep disturbance, impaired memory, and tremor	Often dose dependent, and improve or resolve with dose adjustment
Ocular	<5	Halo vision, especially at night	Corneal deposits the norm; if optic neuritis occurs, discontinue
	1	Optic neuritis	
	>90	Photophobia, visual blurring, and microdeposits	
Heart	5	Bradycardia and AV block	May need permanent cardiac pacing
	<1	Proarrhythmia	May need to discontinue the drug
Genitourinary	<1	Epididymitis and erectile dysfunction	Pain may resolve spontaneously

D_LCO indicates diffusion capacity of carbon monoxide; AST, aspartate aminotransferase; and ALT, alanine aminotransferase.

The time to steady state on a given dose of a drug may exceed 6 months. Likewise, it may take more than 6 months before an adverse drug effect is reversed.

Issues of importance in follow-up are the continued assessment of drug efficacy, titration of drug dose after achieving a steady state, evaluation of adverse and toxic effects, appropriate management of toxic effects, and attention to important drug-drug and drug-device interactions.

When amiodarone first became available in the United States, because of its potential toxicity, electrophysiologists were the only physicians who prescribed the drug. As the drug gained popularity, its use by physicians who do not specialize in arrhythmia management increased. An electrophysiologist is not required for routine long-term follow-up if the treating physician has knowledge of drug doses and adverse effects of amiodarone and has demonstrated expertise in the follow-up of patients taking amiodarone. Whereas such physicians have generally been cardiologists, some internists and family practitioners may have enough experience with, and comfort using, the drug to provide follow-up evaluation. We believe that nonphysician personnel should not provide the follow-up support of patients taking amiodarone.

Routine evaluation requires an office visit to assess new symptoms possibly related to the drug (Table 1), recurrence of arrhythmias, the need for upward or downward drug titration, laboratory testing, and changes in drug therapy. Follow-up should be most intensive initially, especially if dose titration is expected to be necessary or if outpatient oral dose loading is under way. Initial assessment should occur every 3 months for the first year to assess arrhythmia stability and adverse effects, after which follow-up visits should occur every 6 months. Adverse effects are partly dose related, increasing with time of exposure. Some adverse effects (neurologic and gastrointestinal tract toxicity) are clearly dose related, and often occur in the first phases of amiodarone loading. Visual changes ("haloes" around lights) are generally, but not always, dose related. Serious long-term toxicity (the most worrisome of which is pulmonary toxicity) appears related in part to drug dosing. It is arguable whether pulmonary toxicity occurs to a greater degree in patients who have underlying pulmonary disease, such as obstructive pulmonary disease. It can be difficult to distinguish the progression of this underlying disease, however, from the additive effects of amiodarone. Nevertheless, in patients who have underlying pulmonary disease, more careful follow-up is required, even if the patient is taking a low dose (mean dose, <300 mg).[23,24]

To our knowledge, there are few data to document a better outcome with more careful and frequent follow-up, despite the intuitive prudence of this approach. However, early recognition of organ toxicity will expedite early corrective management. The treating physician should educate the patient regarding drug interactions and potential toxicities, and document these discussions in the medical record.

Specific Information to Be Acquired During Follow-up Visits

History. Complaints of fatigue (suggesting bradycardia, AV block, or hypothyroidism), dyspnea or cough (suggesting pulmonary toxicity), palpitations (suggesting hyperthyroidism or recurrence of arrhythmias), syncope, visual changes (including loss of vision), skin changes (including photosensitivity), weight change (suggesting hypothyroidism or hyperthyroidism), paresthe-

Table 2. Routine Laboratory Testing in Patients Receiving Amiodarone*

Type of Test†	Time When Test Is Performed
Liver function tests	Baseline and every 6 mo
Thyroid function tests (T_4 and TSH)	Baseline and every 6 mo
Serum creatinine and electrolytes	Baseline and as indicated
Chest x-ray film	Baseline and then yearly
Ophthalmologic evaluation	At baseline if visual impairment or for symptoms
Pulmonary function tests (including D_LCO)	Baseline and for unexplained dyspnea, especially in patients with underlying lung disease; and if there are suggestive x-ray film abnormalities
ECG	Baseline and every year

**If clinical circumstances warrant, more frequent follow-up will be necessary.*
†T_4 indicates thyroxine; TSH, thyrotropin; D_LCO, diffusion capacity of carbon monoxide; and ECG, electrocardiogram.

Table 3. Major Amiodarone Drug Interactions

Drug	Interaction
Digoxin	Increased concentration and effect with sinus and AV node depression and gastrointestinal tract and neurologic toxicity
Warfarin sodium	Increased concentration and effect
Quinidine, procainamide hydrochloride, or disopyramide	Increased concentration and effect and torsade de pointes ventricular tachycardia
Diltiazem or verapamil	Bradycardia and AV block
β Blockers	Bradycardia and AV block
Flecainide acetate	Increased concentration and effect
Phenytoin	Increased concentration and effect
Anesthetic drugs	Hypotension and bradycardia
Cyclosporine	Increased concentration and effect

sias or weakness (suggesting peripheral neuropathy), changes in drug therapy (especially additional antiarrhythmic drugs, warfarin, β blockers, and digoxin) that require dose adjustment, newly implanted devices (pacemakers, cardioverter-defibrillators, or both), and sleep disturbances should be noted.

Physical Examination. Documentation of vital signs; skin color; regularity of pulse; skin color changes; thyromegaly; dry pulmonary rales; evidence of pulmonary hypertension, left ventricular dysfunction, or both; hepatomegaly; and evidence of neurologic effects (tremor, difficulty with writing, or gait disturbance) should be made. If visual changes are reported, a thorough evaluation by an ophthalmologist, including a slitlamp examination, is required.

Routine Laboratory Evaluation. Baseline tests can include tests measuring serum electrolyte, serum urea nitrogen, and creatinine levels; liver function tests; pulmonary function tests (including the diffusion capacity of carbon monoxide); and thyroid function tests (**Table 2**).[18,25] Baseline pulmonary function tests are especially recommended in patients with underlying lung disease; in otherwise well persons, these tests can be omitted unless new pulmonary complaints arise. A baseline ophthalmologic evaluation should be obtained in any patient who has significant visual abnormalities; it is not required for all patients. The follow-up evaluation should include, at a minimum, a yearly electrocardiogram and a chest x-ray film and semiannually a thyroid profile (thyrotropin and thyroxine levels) and a profile of liver enzymes. Amiodarone levels should be obtained if arrhythmias occur or recur or if new symptoms develop, especially after dose titration or a change in drug formulation (to or from generic preparations); amiodarone levels may help determine if the drug can be titrated downward. Surveillance amiodarone levels are of little use. Drug interactions with amiodarone, especially digoxin and warfarin, must be recognized and monitored as necessary (**Table 3**),[26] since dose adjustments of these agents will be required.

Nonroutine Laboratory Evaluation. Laboratory tests should be ordered sooner than scheduled if there are symptoms suggestive of amiodarone toxicity in a specific organ system.[27] Other testing may be required, depending on changes in drug dose or changes in (or development of) new symptoms. Event monitoring or Holter monitoring may be required if new arrhythmia symptoms occur. Testing of ICDs and pacemakers for threshold changes should be performed if changes in clinical status occur, such as the development of heart failure or intercurrent myocardial infarction.

Referral to an Electrophysiologist

Worsening arrhythmia symptoms is the primary indication to refer the patient to an electrophysiologist. Evidence of amiodarone toxicity requiring changes in drug dosing or drug discontinuation is another important reason to refer to an electrophysiologist. Until the arrhythmia problem stabilizes, the patient may require intensified monitoring, electrophysiologic testing, ablative therapy, or pacemaker or ICD implantation or reprogramming.

ADVERSE REACTIONS

Adverse reactions due to amiodarone should not be unexpected given the drug's complicated pharmacological features, structure, and diverse effects (Table 1). Because of its long half-life (averaging ≈100 days), amiodarone organ toxicity is potentially more severe and difficult to manage than toxic reactions to other drugs with shorter half-lives. Many reactions to amiodarone can be managed with reassurance and observation. Major organ toxicities, however, may be life threatening and may require a more aggressive intervention.

The most common early symptom of pulmonary toxicity is cough, but fever and dyspnea can occur if

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the condition progresses. The incidence is reported to be as high as 10% to 15% in some series,[20,24] but as low as 1% to 2% in others.[22,24,25]

The chest x-ray film commonly shows focal or diffuse infiltrates. A decrease in the diffusing capacity of carbon monoxide from baseline pulmonary function testing supports the diagnosis. Bronchoscopy is useful to exclude other diseases such as tuberculosis and disseminated carcinoma. Foamy macrophages are a manifestation of drug absorption and do not necessarily indicate toxicity. Although amiodarone pulmonary toxicity often responds to corticosteroid administration, the drug usually must be discontinued. Since pulmonary toxicity in its early stages can mimic congestive heart failure, a high index of suspicion for this drug effect is necessary. Failure to diagnose pulmonary toxicity in its early stages can lead to a fatal outcome.

Gastrointestinal tract disturbances such as nausea, anorexia, and constipation are common, especially during the initial loading phase of amiodarone therapy. These symptoms usually abate when the dose is decreased for long-term maintenance. The most feared gastrointestinal tract complications are hepatitis and cirrhosis (incidence, <3%). Hepatitis should be considered when there is an increase in the aspartate aminotransferase or alanine aminotransferase (serum glutamate-pyruvate transaminase, present almost exclusively in the liver) level to at least twice normal levels. In the diagnosis of amiodarone hepatic toxicity, other causes of liver function abnormalities should be considered (other drug reactions and viral and alcoholic hepatitis). A liver biopsy can be considered to determine whether hepatitis or cirrhosis with necrosis is present. Mallory bodies (as with foamy macrophages, previously discussed) are a sign of amiodarone absorption and do not necessarily indicate toxicity. If amiodarone liver toxicity is diagnosed, the drug should be discontinued; amiodarone-induced hepatitis can be fatal.[27]

Thyroid abnormalities occur in up to 22% of patients.[25] Chemical abnormalities of thyroid function can be seen in clinically euthyroid patients and do not require treatment other than monitoring of thyrotropin levels. Hypothyroidism may develop insidiously, with signs and symptoms mistakenly attributed to other causes. For example, bradycardia may be attributed to amiodarone or another drug rather than to hypothyroidism. Conversely, hyperthyroidism may manifest as a worsening of arrhythmias or as weight loss; resting tachycardia is often absent due to the negative chronotropic effect of amiodarone. Although hypothyroidism is easily treated with levothyroxine sodium, hyperthyroidism is difficult to manage. Radioactive ablation with iodine 131 is usually not possible, since the sodium iodide uptake is suppressed by the iodide contained in the amiodarone molecule. Since hyperthyroidism due to amiodarone is usually inflammatory thyroiditis, corticosteroid therapy may be effective. Propylthiouracil and methimazole can be used as stopgap measures. Thyroidectomy is often the best management option since it reverses the hyperthyroidism and allows continuation of the drug, and the iatrogenic hypothyroidism is easily treated.

The slate blue skin discoloration that characterizes long-term amiodarone use is usually most prominent on the face and around the eyes and simply indicates absorption. It can be worsened by sun exposure. Photosensitivity, even if not severe, can be managed by instructing patients to avoid the sun and to use sunblock.

Neurologic complaints include cerebellar ataxia, peripheral neuropathy with paresthesia, sleep disturbance, and, occasionally, impaired memory. These effects are often dose dependent and improve or resolve with minor downward dosage adjustment.

Ocular changes are common. Corneal deposits are the norm, and simply reflect drug absorption. Halo vision is common. Reassurance should be provided. The most serious, albeit rare, complication is optic neuritis. Discontinuation of amiodarone is required if it occurs.

Adverse cardiac reactions are uncommon. Bradycardia is an expected drug effect, and permanent cardiac pacing is occasionally required to support slow heart rates. Similarly, although QT prolongation is to be expected, torsade de pointes VT is rare. Ventricular systolic function is not worsened.

Other drug reactions are rare, eg, epididymitis and erectile dysfunction. Although the drug may need to be discontinued, the pain of the former often resolves independently.

Finally, amiodarone is frequently used with pacemakers and implantable defibrillators. It does not alter the pacing threshold; however, there are important interactions with implantable defibrillators. Amiodarone may not only decrease the rate of VTs to below the device detection rate, but long-term use can also increase the defibrillation threshold. Whenever amiodarone therapy is initiated in a patient who has an implantable defibrillator, electrophysiologic study should be performed to test adverse drug-device interactions after loading is complete.

CONCLUSIONS

Although clinical judgment takes precedence over guidelines for clinical practice, it is nevertheless use-

ful to attempt to provide a consensus approach to the management of patients with specific clinical conditions. The goal of this guideline is to provide such an approach. The physician who prescribes amiodarone and observes patients receiving amiodarone incurs a responsibility, outlined herein. Acceptance of this responsibility should lead to improved patient outcomes, cost savings, and more rational patient care.

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