Interest in amiodarone has increased because of its remarkable efficacy as an antiarrhythmic agent. The purpose of this report is to review what is known about the electrophysiologic actions, hemodynamic effects, pharmacokinetics, alterations of thyroid function, response to treatment of supraventricular and ventricular tachyarrhythmias and adverse effects of amiodarone. Understanding the actions of amiodarone and its metabolism will provide more intelligent use of the drug and minimize the development of side effects.

The mechanism by which amiodarone suppresses cardiac arrhythmias is not known and may relate to prolongation of refractoriness in all cardiac tissues, suppression of automaticity in some fibers, minimal slowing of conduction in fast channel-dependent tissue, or to interactions with the autonomic nervous system, alterations in thyroid metabolism or other factors. Amiodarone exerts definite but fairly minor negative inotropic effects that may be offset by its vasodilator actions.

Amiodarone (Fig. 1) is a benzofuran derivative (1) that was initially developed to treat angina pectoris in patients with coronary artery disease (2). In fact, the drug was moderately successful as an antianginal agent. Further experience with amiodarone revealed it to be a very effective antiarrhythmic agent for treating patients with supraventricular (3) and ventricular (4) tachyarrhythmias. Since our last review of several new antiarrhythmic agents (5), we have treated with amiodarone more than 400 patients referred because of a variety of drug-resistant supraventricular and ventricular tachyarrhythmias. At the time of that review, knowledge of amiodarone's pharmacokinetics, multiple actions and adverse effects was preliminary. We indicated that its antiarrhythmic action persisted 30 to 45 days after discontinuation of drug therapy and mentioned briefly that amiodarone noncompetitively blocked both alpha- and beta-adrenergic receptors, that it increased action potential duration in a variety of tissue types with little or only a slight depressant effect on phase 0 conduction in fast channel tissues and that it decreased the sinus discharge rate, prolonged the QT and AH intervals and lengthened the refractory period of all tissue types. Few adverse effects were listed, including skin discoloration, hyperthyroidism, hypothyroidism, occasional neurologic side effects and corneal microdeposits. In the interval since that study, researchers throughout the world have become interested in this fascinating and unique antiarrhythmic agent, and have dramatically increased our
knowledge of amiodarone’s electrophysiologic actions, pharmacokinetics and clinical effects. The purpose of this review is to summarize some of those data.

Electrophysiologic Actions

The most profound direct electrophysiologic action of amiodarone on cardiac fibers is to prolong repolarization and refractoriness in all cardiac tissue studied, including the sinus node, atrium, atrioventricular (AV) node, His-Purkinje system and ventricle (6). Amiodarone also depresses impulse initiation in the isolated rabbit sinus node (7).

Purkinje system. Recent data (8,9) suggest that amiodarone depresses phase 0 in Purkinje fibers and that this use-dependent effect appears to result from selective blockade of inactivated sodium channels. However, in vitro data of amiodarone should be accepted with caution because of the difficulty of dissolving amiodarone into solution. Nevertheless, the observation is consistent with clinical data. In our experience, orally administered amiodarone prolongs the HV interval in patients by about 15 to 20%.

Sinus and AV nodes. No studies of amiodarone’s action on the slow response action potential have been reported. However, the lack of significant effect of amiodarone on sinus and AV nodal action potentials, other than to prolong repolarization and refractoriness and depress sinus nodal discharge rate, suggest that therapeutic concentrations may not have a major effect in suppressing the slow response (6).

Amiodarone depresses sinus nodal and junctional automaticity and intranodal conduction when injected into the respective sinus and AV nodal arteries in anesthetized dogs. Propranolol or atropine did not influence these changes, but a low calcium concentration in the perfusate enhanced the negative chronotropic effects (10).

Intravenous versus oral administration. Amiodarone given intravenously to animals and human beings produces no significant alterations in the QTc interval despite myocardial concentrations after single intravenous doses in animals that are comparable with those after prolonged oral administration (11). Orally administered amiodarone significantly prolongs the QTc interval (12). Prolongation of AV nodal refractoriness is greater after oral administration than after intravenous administration of amiodarone. A marked increase in the effective refractory periods of all cardiac tissues follows chronic oral therapy while little or no prolongation results after single intravenous bolus injections except in AV nodal fibers. Suction electrodes recording monophasic atrial action potentials have demonstrated prolongation after amiodarone treatment in human beings (13).

Response to adrenergic stimulation. Amiodarone dissolved in ethanol and added to homologous blood plasma noncompetitively antagonizes the chronotropic responses of rabbit atria to isoproterenol (14). It also inhibits noradrenaline-induced contractions of myocardial strips in rats and rabbits, but does not affect potassium-depolarized contractions of mammalian aortic strips. Amiodarone exerts an antisynthetic effect on both alpha- and beta-adrenergic responses to sympathetic stimulation or catecholamine injection (15). Amiodarone also inhibits release of neurotransmitter from presynaptic adrenergic neurons (11).

Hemodynamic Actions

Experimental effects. Amiodarone, 5 mg/kg intravenously in dogs, reduced systemic vascular resistance and mean arterial pressure with no change in left ventricular end-diastolic pressure, first derivative of left ventricular pressure (dP/dt) or contractile force. However, 10 mg/kg increased left ventricular filling pressure and reduced contractility. Intracoronary injections in dogs produced approximately 70% of the peak coronary vasodilator effects of an intracoronary injection of nitroglycerin (6 μg) (11).

Amiodarone given intravenously at a dose of 10 mg/kg in a single bolus 30 minutes after coronary artery occlusion in dogs decreased heart rate, contractility and afterload, and reduced mean aortic pressure, left ventricular peak pressure, left ventricular dP/dt, maximal negative dP/dt but did not change left ventricular end-diastolic pressure. Cardiac output may increase despite the negative inotropic effect because of the more pronounced concomitant reduction of systemic vascular resistance and impedance to left ventricular ejection (16).

Clinical effects. In patients without depressed left ventricular function undergoing diagnostic cardiac catheterization, amiodarone, 5 mg/kg intravenously, reduced mean arterial pressure, left ventricular end-diastolic pressure and systemic vascular resistance and slightly increased cardiac index. Coronary vascular resistance decreased and coronary sinus flow increased. Despite the decrease in systemic vascular resistance, a reflex increase in heart rate did not occur, consistent with the drug’s antidrenergic effects (17).

Oral doses of the drug sufficient to control cardiac arrhythmias do not depress left ventricular ejection fraction measured by radionuclide ventriculography. Because amiodarone rarely aggravates hemodynamic function even in patients with compromised left ventricular contractility, minor negative inotropic effects may be offset by the potent vasodilator properties of the drug even in patients with compromised left ventricular contractility. However, in patients
with compensated cardiac failure critically dependent on augmented sympathetic drive, the nonspecific antisypathetic effect of amiodarone may produce hemodynamic deterioration (11).

In patients with depressed left ventricular function and recurrent ventricular tachycardia, amiodarone given intravenously at a loading dose of 5 mg/kg body weight over 20 minutes resulted in a linear decrease in heart rate, a reduction in stroke work index and cardiac index, without any significant change in systemic vascular resistance or pulmonary capillary wedge pressure. Depression of left ventricular function was mild and transient and well tolerated, except in two patients with overt heart failure and severely depressed left ventricular ejection fraction, who developed profound hypotension. Transient deterioration of left ventricular contractility was more apparent in patients with severely depressed left ventricular function, probably resulting from the negative inotropic effects of amiodarone. In most patients this depression was transient and not severe. The decrease in contractility that tends to decrease cardiac output appears to be balanced by afterload reduction which increases cardiac output, resulting in either no change or only a slight transient deterioration of left ventricular function (18).

After protracted oral amiodarone therapy, no significant change in left ventricular ejection fraction measured by radionuclide ventriculography has been noted. Although well controlled studies on the hemodynamic effects of chronically administered oral amiodarone are lacking, present data (19) suggest that the drug does not have severe negative inotropic effects of clinical significance in most patients.

From these data it is apparent that amiodarone may be administered to patients with compromised left ventricular function. In addition, amiodarone may be useful in patients who have coronary disease and exercise-induced angina (2) or even atypical angina (20).

Pharmacokinetics

Bioavailability, clearance rate and half-life. Amiodarone has a reduced clearance rate, large volume of distribution, low bioavailability and a long half-life. The low bioavailability may relate to incomplete intestinal absorption while the larger volume of distribution and reduced clearance contribute to the long elimination half-life. Amiodarone may be released slowly from a reservoir or poorly perfused deep compartment such as fat into the plasma. After intravenous administration of 400 mg amiodarone to healthy young male volunteers, total plasma clearance was about 8.5 liters/h, total blood clearance about 12 liters/h, with a steady state distribution volume of approximately 5,000 liters. Terminal elimination half-life was 25 days after single dosing and oral bioavailability 35%. Renal elimination of both amiodarone and its metabolite desethylamiodarone was negligible. Clearance of amiodarone decreases with time and it is possible, based on the fact that amiodarone decreases the clearance of other drugs, that amiodarone decreases its own clearance. Terminal elimination half-life of the major metabolite, desethylamiodarone, was similar to that of the parent compound (21).

Plasma concentration and elimination half-life. In 170 patients receiving maintenance amiodarone therapy, a daily dose of 200 mg produced a plasma concentration of approximately 1.0 μg/ml. A dose of 400 mg daily resulted in plasma concentrations of approximately 2.0 μg/ml and 600 mg, approximately 3.5 μg/ml. Terminal elimination half-life after cessation of chronic therapy was about 53 days for the parent compound and 61 days for the metabolite. Patients appear to have a longer elimination half-life than volunteer subjects, but the range is wide: 13 to 107 days after chronic therapy (21). Both parent drug and metabolite have been measured in plasma more than 9 months after cessation of therapy. The long terminal phase of elimination prolongs the time taken to attain steady state tissue concentrations. An excess of 10 days may be required to achieve equilibration in the slowly penetrated tissues. Of interest, in the first few days after cessation of therapy, plasma concentrations decreased comparatively rapidly, followed by a rebound peak 12 to 21 days after stopping treatment. This biphasic elimination pattern of amiodarone, possibly due to rapid clearance from well perfused tissues of the central compartment with slower elimination from poorly perfused tissue compartments, may necessitate frequent maintenance dosage intervals despite such a prolonged terminal elimination half-life. The concentration of the desethylamiodarone metabolite exceeds that of amiodarone in all tissues except those in which the amiodarone concentrations are high (for example, fat, approximately 300 mg/kg wet weight) where the concentration of amiodarone exceeds the concentration of the metabolite (21).

Loading dose and daily dose schedule. These data suggest that a large loading dose should be used when beginning amiodarone therapy because the large volume of distribution would be expected to delay the time to achieve minimal effective drug concentrations within the body and thus delay the time to onset of clinical efficacy. A loading regimen appears to decrease the time of onset of antiarrhythmic action (22).

As might be expected, a daily dose schedule of 1,600 mg/day produces significantly higher drug concentrations than 800 mg/day. After 15 days, patients receiving 800 mg/day achieved an amiodarone plasma concentration of 1.7 μg/ml while those receiving 1,600 mg/day had 2.7 μg/ml. The ratio of desethylamiodarone to amiodarone in both plasma and red cells increased progressively with time, reaching about 0.5 in plasma but 1.5 to 2 in red cells after 15 days for both doses. During chronic amiodarone administration, with doses of 200 to 600 mg/day, the mean ratio
of desethylamiodarone to amiodarone increased to 0.78 in plasma and to 2.4 in red blood cells samples. Plasma amiodarone concentrations after 200, 300, 400 and 600 mg amiodarone/day long-term were 1.4, 1.5, 2.3 and 2.9 µg/ml, respectively. These data indicate that a direct relation exists between size of the daily loading dose of amiodarone and plasma or red blood cell concentration. The rate of formation of desethylamiodarone appears to be time dependent. A linear correlation results between plasma concentrations of drug and metabolite (23).

Distribution, equilibrium and dosage. Approximately 20 to 60% of an oral dose of amiodarone enters the systemic circulation with maximal plasma concentration achieved 4 to 5 hours after drug ingestion. Amiodarone is then distributed throughout the body to achieve an equilibrium between tissues and plasma. The time course of the equilibrium varies greatly among different tissues (21,24,25).

Amiodarone exhibits heterogeneous distribution and equilibrium and is better described by models with three or four compartments. A compartment is a pharmacokinetic rather than an anatomic entity, reflecting the characteristics of drug uptake and release by a group of tissues in the body. Tissues with different characteristics would be included in different compartments. Amiodarone may have a "deep" peripheral compartment such as fat or other poorly perfused tissues having an affinity for lipid-soluble drugs, with which equilibrium is achieved very slowly. The concentration of amiodarone in the central (well perfused) compartment increases rapidly to reach steady state levels within 1 day while the accumulation of drug in peripheral compartments is slow, requiring several days to a week to reach steady state levels. Based on known pharmacokinetics, a theoretical regimen calculated to achieve a plasma amiodarone concentration of 1.5 µg/ml, assuming approximately 50% bioavailability, might be 2 g during the first day and then 1,400 mg/day for three days, 1,000 mg/day for one week, 800 mg/day for 2 weeks, 600 mg/day for 4 weeks and then 400 mg alternating with 600 mg/day maintenance. Amiodarone would be given in divided doses of 600 mg or less (26).

Chronic therapy: plasma concentrations and dosage. Because amiodarone pharmacokinetics may change with time, monitoring plasma concentrations during chronic treatment may give important information about the relation between drug concentration and effect and allow development of more definite guide lines for safe chronic therapy. The wide range of reported bioavailability could lead to toxic accumulation of drug in some patients. Plasma concentrations may not be helpful or may be misleading during the 4 to 6 week loading period at the beginning of treatment (26).

The therapeutic level of serum concentrations varies, but appears to range between 1.0 and 3.5 µg/ml. In one study (27) of 96 patients with life-threatening ventricular arrhythmias and 77 patients with a variety of supraventricular tachyarrhythmias resistant to conventional antiarrhythmic agents in therapeutic doses, amiodarone was judged effective in approximately 80% of patients followed up for 10 months by preventing recurrence of symptoms of the arrhythmia or by producing greater than 80% decrease of high grade ventricular ectopic activity during ambulatory electrocardiographic monitoring. Maintenance amiodarone serum concentrations ranged from 0.6 to 2.8 µg/ml (mean 1.6 in the responders with a wide intersubject variation of serum concentrations for a given dose of amiodarone). Arrhythmia relapses occurred in nine patients when their serum concentration decreased to less than 1.0 µg/ml. In eight of these patients, reinstitution of higher amiodarone dosages and elevation of serum amiodarone concentration again suppressed their arrhythmias. Thus, there appears to be a good relation between dosage and steady state concentration of amiodarone. However, the reported data (27) indicate considerable overlap of concentrations both for therapeutic efficacy as well as for those concentrations associated with toxicity.

**Treatment of Arrhythmias**

### Supraventricular Tachyarrhythmia

Amiodarone is effective therapy for patients who have a wide variety of supraventricular tachyarrhythmias. As with ventricular tachyarrhythmias the exact percentage of success varies, influenced in part by whether a group of patients represent a selected group with drug-resistant arrhythmias. Nevertheless, data from sufficiently diverse studies indicate that amiodarone effectively suppresses recurrences of supraventricular tachycardia in 80% or more of the patients treated (3,4,28,29).

**Dosage and effectiveness.** In contrast to patients receiving the drug for ventricular arrhythmias, lower loading and maintenance doses appear to be necessary to control supraventricular tachycardias (30,31). For example, in one study, suppression of supraventricular arrhythmias required 280 to 350 mg/day versus 400 to 440 mg/day for ventricular arrhythmias (30). In another (29), about 50% of 121 patients needed 200 mg/day of amiodarone to suppress recurrences of supraventricular tachyarrhythmias while only 6% required a 600 mg daily maintenance dose. No differences in serum concentration of the parent drug were noted among responders and nonresponders. Side effects were generally, but not invariably, associated with a higher average serum concentration (2.3 µg/ml) than necessary for control of arrhythmia. However, there was much overlap in dose and in serum concentration between those with and without side effects. Of 95 patients with atrial fibrillation or atrial flutter, 74 had an effective response (arrhythmia prevented for at least 6 months) and six had a partial response (recurrence
but at longer intervals with episodes more abbreviated and self-terminating). In 15 patients, amiodarone was ineffective. In 26 patients who had a presumed reentrant supraventricular tachycardia, in 9 associated with an accessory pathway, amiodarone was effective in 24, partially effective in 1 and ineffective in 1. Thus, 105 (86.7%) of 121 patients receiving amiodarone experienced complete or partial control of their clinical arrhythmia. Ninety-eight patients (81%) had complete suppression of symptomatic recurrence over an average follow-up of 27 months. Seven patients had a partial response, 16% were failures and significant side effects required discontinuation of therapy in eight patients (29).

**Wolff-Parkinson-White syndrome with circus movement tachycardia.** In 30 patients with Wolff-Parkinson-White syndrome and the usual (orthodromic) form of circus movement tachycardia receiving a total of 11.2 to 14 g of amiodarone over 6 to 8 weeks of therapy (32), refractory periods of the atrium, AV node, His-Purkinje system, ventricle and accessory pathway prolonged. Programmed stimulation of the heart in these 30 patients revealed that the arrhythmia could no longer be initiated in nine due to marked prolongation of the refractory period or block in the accessory pathway retrogradely (four patients), block in the AV node (four patients) or block between the His bundle and ventricle (one patient). Thus, the weak link in the reentry circuit after amiodarone administration differed from patient to patient. Four patients showed spontaneous termination of circus movement tachycardia that did not occur before amiodarone therapy, due to block in the AV node (two patients) or accessory pathway (two patients). In the 23 patients in whom circus movement tachycardia could still be initiated after amiodarone treatment, the rate of the tachycardia slowed with a mean increase in RR interval of 85 ms (32). Although tachycardia was still initiated in 21 patients by programmed electrical stimulation, follow-up (8 to 70 months, mean 40) revealed that spontaneous episodes of tachycardia occurred in only four patients. This finding suggests that the therapeutic efficacy of amiodarone in these patients may be based, in part, on prevention of tachycardia-initiating premature beats. The weekly dose of amiodarone required to control the arrhythmia was 500 mg in four patients, 700 to 1,400 mg in 21 patients and more than 1,400 mg in only two patients. Side effects did not necessitate termination of amiodarone administration in any patient (32).

**Wolff-Parkinson-White syndrome with atrial fibrillation.** In these patients, symptoms produced by the arrhythmia primarily relate to the duration of the anterograde refractory period of the accessory pathway, which in large part determines the ventricular rate. The extent of lengthening of the duration of the refractory period of the accessory pathway anterogradely after amiodarone is related to the duration of the refractory period before treatment. When the duration of the control refractory period is short, amiodarone lengthens it very little. Complete anterograde block in the accessory pathway after ajmaline or procainamide administration predicts an increase of 100 ± 85 ms in the anterograde effective refractory period of the accessory pathway after amiodarone administration, which is twice the increase observed in patients with a negative ajmaline or procainamide test. However, amiodarone may also be efficacious by preventing recurrences of the arrhythmia. For example, amiodarone administered to 17 patients with recurrent episodes of atrial fibrillation terminated recurrences in 13 patients (mean follow-up 50 months) while 4 patients continued to have paroxysmal episodes of atrial fibrillation requiring surgical interruption of the accessory pathway in 2 (33).

**Resistant supraventricular tachycardia.** AV nodal reentrant tachycardia resistant to other antiarrhythmic drugs may respond chronically to relatively small doses of amiodarone (4,28,34). Patients with supraventricular tachyarrhythmias more difficult to control may be those who have so-called " incessant" supraventricular tachycardia related to a concealed accessory pathway and those with a " permanent" form of reciprocating tachycardia (31). Patients with atrial fibrillation difficult to control may be those who have episodes of atrial fibrillation precipitated during physical exertion that tend to recur during activity rather than during sleep or rest (35). In treating this form of atrial fibrillation, beta-adrenergic receptor blocking drugs may be more effective than amiodarone. In some patients after control of the atrial fibrillation for several weeks, the tendency to develop new episodes may be reduced so that much lower doses of amiodarone may provide subsequent control (31).

**Ventricular Tachyarrhythmia**

Data from a large number of studies attest to clinical efficacy of amiodarone in suppressing spontaneous ventricular tachyarrhythmias. Amiodarone consistently reduces the number of spontaneous premature ventricular complexes and episodes of ventricular tachycardia determined by ambulatory recordings. The percent reduction in ventricular ectopic complexes varies in different studies but generally exceeds 80%. Larger maintenance doses of amiodarone may be required to suppress episodes of ventricular tachycardia than to suppress premature ventricular complexes (31).

**Therapeutic latency.** When amiodarone is discontinued after a given time, the antiarrhythmic protection lasts for several days, weeks or even months (4). A therapeutic " latency" exists before the maximal antiarrhythmic effects (as well as many adverse effects) are obtained with amiodarone. Initial therapeutic latency varies in most cases from 5 to 15 days but full suppression of arrhythmia may not be reached until 15 to 30 days, or more, of treatment. Interestingly, the average heart rate at rest commonly continues to slow until the third and sometimes even the fourth or fifth month.
of therapy, suggesting a continued “building up” of amiodarone effects, at least on sinus rate. Patients with sustained recurrent symptomatic ventricular tachycardia may require at least 8 to 10 days of drug administration to achieve control of the arrhythmia (12,31). Clinical studies suggest that the more difficult it is to control a given arrhythmia, the longer the latency to achieve suppression and shorter the persistence of effects after drug discontinuation. Conversely, in patients with more easily controlled arrhythmias, latency is shorter, duration of drug effects is longer, and often less drug is required to maintain suppression of the arrhythmias. The latency appears to be short in children (36).

**Results in recurrent ventricular tachycardia.** We have recently evaluated (37) our study group of 196 patients (mean age 56 years; 154 men) who began amiodarone treatment for recurrent ventricular tachycardia or ventricular fibrillation and who had at least 1 month of follow-up before December 31, 1982. One hundred twenty-nine patients had ischemic heart disease and 35 patients had idiopathic dilated cardiomyopathy. The remainder had a variety of diagnoses. On the basis of New York Heart Association criteria, 25 patients were in functional class I, 112 in class II, 54 in class III and 5 in class IV according to symptoms and signs of congestive heart failure. Recurrent sustained ventricular tachycardia, defined as ventricular tachycardia that produced syncope, required electrical cardioversion or lasted longer than 30 seconds, was present in 95 patients. In 44 patients, recurrent ventricular tachycardia was nonsustained. Fifty-seven patients had experienced one or more episodes of cardiac arrest due to ventricular fibrillation that required cardiopulmonary resuscitation. Each patient had received 2 to 10 (mean 4.4 ± 1.9) drug trials before amiodarone treatment. Of 863 prior drug trials, 798 had failed because of recurrence of ventricular tachycardia or ventricular fibrillation and 105 patients had required cardioversion or defibrillation during prior drug trials (37).

Amiodarone was administered at a dose of 800 mg/day for 4 to 8 weeks. The dose was decreased at 3 month intervals to 200 to 600 mg/day if the arrhythmia remained suppressed. Patients who entered the investigation during the last 6 months of the study period received an initial amiodarone dose of 1,600 mg/day for the first 2 weeks of treatment, then 800 mg/day with gradual reduction to 200 to 600 mg/day.

During a mean follow-up time of 16.2 ± 13.0 months (range 1 to 57), 126 (64%) of 196 patients continued to receive amiodarone treatment, including 35 (61%) of 57 who had recurrent ventricular fibrillation, 59 (62%) of 95 who had recurrent sustained ventricular tachycardia and 32 (73%) of 44 who had recurrent nonsustained ventricular tachycardia. The results after the initial month of amiodarone treatment are outlined in Table 1, while the outcome of long-term (16.2 ± 13.0 months) amiodarone treatment in 177 patients is outlined in Table 2. No recurrence of spontaneous ventricular tachycardia or ventricular fibrillation was evident in 139 patients, of whom 112 have continued long-term treatment. Ventricular tachycardia or ventricular fibrillation recurred in 38 patients but amiodarone was continued in 17 of these patients, usually along with a dosage change, addition of another drug or insertion of an electrical device. During continued follow-up of these 17 patients, 3 died from congestive heart failure that antedated onset of amiodarone treatment and 14 have continued amiodarone treatment.

Of 126 patients receiving long-term amiodarone treatment, 41 have had the following antiarrhythmic drugs added to amiodarone: procainamide in 12, quinidine in 10, 12, disopyramide in 5, mexiletine in 2, mexiletine and propranolol in 1, propranolol alone in 2, propranolol and mexiletine in 1 and propafenone in 1. In no patient did a drug combination appear to result in exacerbation of ventricular arrhythmia or congestive heart failure but doses of both amiodarone and the added drug were reduced, often by 50%. During the course of treatment, amiodarone was discontinued in 12 patients because of noncardiac adverse effects: pulmonary toxicity in 5, nausea and anorexia in 4, tremor and ataxia in 1, urinary retention in 1 and hyperthyroidism in 1 patient. A permanent pacemaker was implanted in four patients who developed symptomatic bradyarrhythmias during amiodarone treatment (37).

Amiodarone treatment appeared to exacerbate ventricular arrhythmia in nine patients (Table 3). Patient 5, who was taking digoxin, was the only patient receiving other cardioactive drugs. In Patients 2, 8 and 9, multiple other antiarrhythmic drugs were associated with exacerbation of arrhythmias. In all nine patients, the amiodarone-associated arrhythmias resolved within 2 to 3 days after discontinuation of amiodarone (37). Arrhythmias associated with amiodarone treatment have been noted by others as well (38–42), but their frequency appears to be less than with most other antiarrhythmic agents.

**Role of electrophysiologic studies.** In our patients electrophysiologic studies were performed after at least 2 weeks of amiodarone treatment in 101 patients who had ventricular tachycardia induced at control study and in 17 patients who did not undergo a control study before drug administration (37). Of the 101 patients who had serial electrophysiologic studies, amiodarone was discontinued in 2 patients after induction of sustained ventricular tachycardia. In 15 patients, including 2 who had amiodarone combined with quinidine because of spontaneous ventricular tachycardia, amiodarone prevented ventricular tachycardia induction at repeat electrophysiologic study. None of these 15 patients had recurrent ventricular tachycardia during long-term amiodarone treatment.

In the other 84 serially studied patients and in 17 patients who did not have a control electrophysiologic study, programmed electrical stimulation during amiodarone treatment...
Table 1. Outcome of Initial Treatment of Ventricular Arrhythmias With Amiodarone for 1 Month in 196 Patients

<table>
<thead>
<tr>
<th>Group</th>
<th>Total Patients (no.)</th>
<th>Response</th>
<th>Treatment</th>
<th>Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>107</td>
<td>No spontaneous VT or VF</td>
<td>Amiodarone continued</td>
<td>107</td>
</tr>
<tr>
<td>II</td>
<td>73</td>
<td>Recurrent spontaneous VT or VF</td>
<td>Amiodarone continued alone</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Antiarrhythmic agent added</td>
<td>51</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Amiodarone discontinued</td>
<td>14</td>
</tr>
<tr>
<td>III</td>
<td>13</td>
<td>Treatment change due to VT induced at EP study</td>
<td>Antiarrhythmic agent added</td>
<td>11</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Amiodarone discontinued</td>
<td>2</td>
</tr>
<tr>
<td>IV</td>
<td>3</td>
<td>Amiodarone discontinued</td>
<td>Adverse side effects</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Death from congestive heart failure</td>
<td>1</td>
</tr>
</tbody>
</table>

EP = electrophysiologic; VF = ventricular fibrillation; VT = ventricular tachycardia. Adapted from Heger JJ, Prystowsky EN, Zipes DP (37) with permission of the American Heart Journal.

Table 2. Outcome of Long-Term Treatment of Ventricular Arrhythmias With Amiodarone

<table>
<thead>
<tr>
<th>Group</th>
<th>Total Patients (no.)</th>
<th>Response</th>
<th>Treatment</th>
<th>Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>139</td>
<td>No spontaneous VT or VF</td>
<td>Amiodarone continued</td>
<td>112</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Amiodarone discontinued due to</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Adverse side effects</td>
<td>16</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Death from CHF</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Noncardiac death</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Sudden cardiac death</td>
<td>15</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Recurrent VT or VF</td>
<td>Amiodarone discontinued</td>
<td>6</td>
</tr>
<tr>
<td>II</td>
<td>38</td>
<td></td>
<td>Amiodarone continued</td>
<td>17*</td>
</tr>
</tbody>
</table>

*Three of these patients died from congestive heart failure.
CHF = congestive heart failure; VF = ventricular fibrillation; VT = ventricular tachycardia.
Reproduced from Heger JJ, Prystowsky EN, Zipes DP (37) with permission of the American Heart Journal.

Table 3. Amiodarone-Associated Exacerbation of Ventricular Arrhythmias

<table>
<thead>
<tr>
<th>Patient</th>
<th>Pretreatment Arrhythmia</th>
<th>Amiodarone Treatment (wks)</th>
<th>Arrhythmias</th>
<th>Successful Treatment</th>
<th>Follow-up (mo)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>VT-S</td>
<td>4</td>
<td>Polymorphic VT; syncope</td>
<td>Mexiletine</td>
<td>6</td>
</tr>
<tr>
<td>2</td>
<td>VF</td>
<td>2</td>
<td>Incessant VT-NS</td>
<td>Propranolol</td>
<td>14</td>
</tr>
<tr>
<td>3</td>
<td>VT-S</td>
<td>2</td>
<td>Incessant VT-S; multiple DC shocks</td>
<td>Quinidine</td>
<td>14</td>
</tr>
<tr>
<td>4</td>
<td>VT-NS</td>
<td>2</td>
<td>VF</td>
<td>Mexiletine</td>
<td>19</td>
</tr>
<tr>
<td>5</td>
<td>VT-S</td>
<td>2</td>
<td>VF</td>
<td>Mexiletine</td>
<td>33</td>
</tr>
<tr>
<td>6</td>
<td>VT-S</td>
<td>2</td>
<td>Continuous VT; temporary pacemaker</td>
<td>Tocainide</td>
<td>18</td>
</tr>
<tr>
<td>7</td>
<td>VT-S</td>
<td>2</td>
<td>VF</td>
<td>Mexiletine</td>
<td>39</td>
</tr>
<tr>
<td>8</td>
<td>VT-NS</td>
<td>2</td>
<td>Incessant VT-S</td>
<td>Propranolol</td>
<td>8</td>
</tr>
<tr>
<td>9</td>
<td>VT-S</td>
<td>2</td>
<td>Incessant VT-S</td>
<td>Tocainide + propranolol</td>
<td>40</td>
</tr>
</tbody>
</table>

DC = direct current; VF = ventricular fibrillation; VT-NS = nonsustained ventricular tachycardia; VT-S = sustained ventricular tachycardia.
Adapted from Heger JJ, Prystowsky EN, Zipes DP (37) with permission of the American Heart Journal.
induced ventricular tachycardia but amiodarone treatment was continued. Of these 101 patients, 80 have continued long-term amiodarone treatment for a mean follow-up period of 14.2 months with no recurrence of spontaneous ventricular tachycardia. Ventricular tachycardia or ventricular fibrillation recurred in the other 21 patients at a mean follow-up period of 5.6 ± 5.1 months. Therefore, amiodarone infrequently prevented induction of ventricular tachycardia by premature ventricular stimulation, but long-term amiodarone treatment successfully prevented recurrences in the majority of patients who had ventricular tachycardia induced during initial amiodarone administration (37).

It is possible that the maximal antiarrhythmic effects of amiodarone were not evident when electrophysiologic studies were performed 2 to 4 weeks after starting treatment. However, other studies (43–45) in which programmed electrical stimulation was performed at longer time intervals after initiation of amiodarone treatment have also confirmed the observation that ventricular tachycardia induction during electrophysiologic study does not preclude a favorable long-term course.

**Predictors of long-term success.** Electrophysiologic variables other than the ability to induce ventricular tachycardia may predict long-term success of amiodarone treatment (46). By using discriminant function analysis, variables that predicted long-term success of amiodarone treatment despite induction of ventricular tachycardia at electrophysiologic study were the change in repetitive ventricular response status, change in the mode of induction of ventricular tachycardia and change in right ventricular effective refractory period or QT interval (37).

Some studies (47) support the use of electrophysiologic testing to predict the clinical response in patients who have ventricular tachyarrhythmias treated with amiodarone. In 69 consecutive patients with recurrent sustained ventricular tachycardia (57 patients), symptomatic nonsustained ventricular tachycardia (< 30 seconds in duration, 7 patients) or ventricular fibrillation (5 patients), programmed ventricular stimulation using single, double and triple extrastimuli delivered at multiple sites and cycle lengths was used to initiate tachycardia. Patients were tested 11 to 15 days after receiving amiodarone, essentially 800 mg/day. In 22 patients ventricular arrhythmias were no longer inducible (Group 1), while 47 patients still had the arrhythmia induced (Group 2). In Group 1, 18 patients received amiodarone and another antiarrhythmic drug. There have been no recurrences of ventricular arrhythmia in these 22 patients; 4 died of nonarrhythmic causes. In Group 2, 43 patients received amiodarone alone and 4 patients received amiodarone and a second antiarrhythmic drug. Fifteen have had a recurrence of ventricular tachycardia or ventricular fibrillation. Three patients had out of hospital cardiac arrest and two additional patients had syncope but without documented arrhythmia. After a mean follow-up of 12 months, five patients in Group 2 died, three of nonarrhythmic causes and two of sudden death.

It appears clear that when evaluating antiarrhythmic drugs other than amiodarone, continued inducibility of the arrhythmia during electrophysiologic study usually predicts a high likelihood of recurrence (75 to 90%) (48), whereas recurrence rate is lower (10 to 50%) in patients receiving amiodarone with similar electrophysiologic results. The explanation for this difference is unclear. In some patients this may be due to suppression of premature complexes that precipitate the tachyarrhythmia.

**Adverse Effects**

**General Incidence**

**Photosensitivity.** In 140 patients treated with amiodarone (mean daily dose 360 mg, range 100 to 1,200) over a 5 year period (average duration of follow-up, 2 years), photosensitivity varying from increased propensity to sun tan during the summer months to intense burning, erythema and swelling of sun-exposed areas was the most common adverse reaction (57%), based on data from patients responding to a questionnaire (30). Neither dosage nor plasma drug concentrations proved useful in distinguishing patients with and without photosensitivity. Dose reduction partially alleviated this reaction in some patients while others obtained some relief with sun screen barrier creams. No patients stopped the drug because of this reaction. Two patients developing slate-gray pigmentation had been using 600 mg/day for 5 and 2 years, respectively, and had plasma concentrations of amiodarone of 3.1 μg/ml. Pigmentation decreased gradually over a 6 to 12 month period after discontinuation of therapy. Six patients in the first weeks of therapy developed an erythematous, pruritic rash predominantly over the trunk.

**Thyroid, gastrointestinal, ocular and neuromotor effects.** Two patients developed obvious clinical findings of hypothyroidism. Thirty-one percent of patients reported gastrointestinal effects, including nausea and loss of appetite during the initial loading phase and alterations in bowel habits with a tendency to subsequent constipation. Biochemical alterations in hepatic function tests were common although no patient developed clinically evident hepatic dysfunction.

One patient developed pulmonary interstitial changes but the relation to amiodarone was questionable.

**Corneal microdeposits** were found as early as 10 days after starting amiodarone and were present in all patients examined after 1 month of therapy. Two patients complained of blue-green halos on looking at bright lights that disappeared within 2 months of dose reduction. Because percents are based on response to a questionnaire, some bias must be anticipated because patients experiencing problems
may have a greater motivation to respond to the questionnaire than those who are asymptomatic (30).

In another study of 51 patients (43), 2 patients developed clinical hepatitis while taking amiodarone. No patient developed peripheral neuropathy; however, 30% had a fine tremor of hands, 28% had sleep disturbance and 14% had headaches. All complaints responded to a reduction in dosage. Proximal muscle weakness occurred in eight patients during the initial loading phase. In this regard, a sensorimotor neuropathy has been reported with segmental demyelination of nerve fibers by histologic examination (49,50). Resolution of the neuropathy occurs with discontinuation of treatment, but his may be slow and incomplete.

**Long-term side effects.** In a study (51) of 70 consecutive patients treated with oral amiodarone, 1,200 mg for 7 days and 600 mg daily thereafter, and having at least 6 months of follow-up (mean 11), side effects occurred in 93% of patients but only 19% had to discontinue their medication. Fifty-six patients had gastrointestinal side effects, most commonly constipation. All but one patient eventually developed corneal microdeposits. Cardiovascular side effects were uncommon, while symptomatic pulmonary side effects occurred in seven patients with pulmonary toxicity in five. Neurologic side effects occurred in 52 patients, most commonly tremor and ataxia. Thyroid dysfunction occurred in 3 patients and 32 patients had skin abnormalities.

**Relation to red blood cell drug and metabolite concentrations.** In our study (23), adverse side effects during chronic amiodarone therapy were related most strongly to red blood cell drug and metabolite concentrations. The group with adverse side effects had significantly higher red blood cell concentrations of amiodarone (1.5 versus 0.75 μg/ml, probability [p] < 0.001) than the patients free of adverse effects. The occurrence of pulmonary toxicity from amiodarone was not related to duration of treatment or cumulative dose of drug in eight patients who had received amiodarone from 2 weeks to 30 months with a total cumulative dose ranging from 11.2 to 396 g. At the time of development of pulmonary toxicity, each patient was receiving 800 mg/day. Blue skin discoloration occurred in 17 (36%) of 53 patients treated longer than 17 months and may relate to the cumulative dose of amiodarone. Lung concentration of amiodarone in a single patient with pulmonary toxicity was considerably higher than that found in an unaffected patient (23). Patients who have skin discoloration have higher concentrations of amiodarone and desethylamiodarone in affected areas compared with unaffected areas (21). Four patients required pacemakers for symptomatic bradycardia.

**Drug Interactions**

**Warfarin.** Amiodarone interacts with other drugs. It potentiates the anticoagulant effect of warfarin (52–55). Prolongation of prothrombin time may occur as early as 3 to 4 days after starting amiodarone therapy or be delayed as long as 3 weeks. The potentiating effect persists for weeks or months (56). The effect of amiodarone on prothrombin activity appears to be dose-dependent, but the mechanism is not clear. Maintenance doses of warfarin may be reduced by a third or a half when amiodarone is begun. Amiodarone may also influence heparin activity (55).

**Digoxin.** Amiodarone increases serum digoxin concentration within 24 hours after dosing. Digoxin concentrations rise linearly for 6 to 7 days and then plateau. The magnitude of the interaction appears to be dose-related (57) and correlates with plasma concentration of amiodarone (58). The mechanism is not clear but may be due to reduction of elimination of digoxin by renal tubular secretion. Other mechanisms include a decrease in extrarenal excretion and tissue displacement of digoxin by amiodarone. Serum digoxin levels usually double when amiodarone is given (55).

**Other antiarrhythmic agents.** Amiodarone can interact with other antiarrhythmic agents and can aggravate or initiate serious arrhythmias such as torsade de pointes, but appears to do so less often than most other class I antiarrhythmic drugs (37–42). Amiodarone may increase the serum concentration of quinidine along with an increase in QT prolongation in patients treated with amiodarone who are already receiving quinidine (59). Similar increases in aprindine (60) and procainamide (61) concentrations have been found when these drugs were given in conjunction with amiodarone. The dose of the second antiarrhythmic agent probably should be reduced by 50%.

**Amiodarone may have additive effects with drugs that exert similar actions, such as producing sinus nodal slowing during concomitant administration of beta-adrenergic receptor blockers (62) or slow calcium channel blockers. Hypotension and atropine-resistant bradycardia may occur during surgery (63).**

**Ocular Side Effects**

Ocular deposits are bilateral and symmetrical, and depend on dosage and duration of treatment. In one study (64), 98% of 103 patients treated with oral amiodarone and followed up for periods of longer than 3 months developed the characteristic keratopathy. Earliest changes resemble a gray or brownish linear mark on the cornea running approximately horizontally at about the junction of the middle and lower thirds of the cornea and not reaching the limbus. The deposits then become more granular, grayish or brown tinted lines radiating outward in a curved fashion from the center point of the interpalpebral zone toward and often reaching the limbus. On further deposition, more lines form in similar but increasingly complex patterns resembling a vortex or whorl. Finally, more advanced changes produce a granular "dusting" of the whole corneal epithelium (64). Changes are superficial and localized to the corneal epithelium.
Pulmonary Side Effects

Pulmonary alveolitis. Of the extracardiac side effects produced by amiodarone, the most serious is pulmonary alveolitis (12,66-70). In our study of 196 patients (37), amiodarone treatment resulted in pulmonary toxicity in 7, as evidenced by diffuse pulmonary interstitial infiltrates consistent with fibrosing alveolitis in 6 patients and by a strongly positive gallium radionuclide lung scan in the other patient. These seven patients had received amiodarone for a period ranging from 2 weeks to 30 months before the recognition of pulmonary abnormalities. Pulmonary abnormalities were discovered at postmortem examination in one patient who died from congestive heart failure, and in another patient pulmonary abnormalities were noted 2 weeks after amiodarone was discontinued because of recurrent ventricular tachycardia. After amiodarone was discontinued, one patient died from progressive pulmonary insufficiency and heart failure and one patient died secondary to heart failure and sepsis. Three patients were treated with glucocorticoids, one patient received no immunosuppressive treatment and all four have had symptomatic and roentgenographic improvement.

Clinical features. Patients with pulmonary toxicity complain of exertional dyspnea, nonproductive cough and weight loss but only occasionally grade fever. Pleuritic pain is uncommon. Physical findings usually reveal basilar rales or decreased breath sounds and rarely a pleural friction rub. X-ray findings generally indicate diffuse bilateral interstitial changes and patchy or diffuse alveolar infiltrates, commonly suggesting the presence of pulmonary edema, pneumonitis or tuberculosis. Rarely pleural effusion or areas of pleural thickening may be found. Patients may demonstrate hypoxia, restrictive changes with reduction in total lung capacity and diffusion abnormalities (68). In a preliminary study (67), serial changes in pulmonary function tests provided no predictive evidence for the development of pulmonary toxicity.

Pulmonary changes have been noted to resolve on withdrawal of amiodarone alone or on reduction of the dose. Improvement has occurred with and without the addition of steroid therapy. One patient who initially developed pulmonary complications while receiving amiodarone had regression of changes when the drug was discontinued and developed no new changes when the drug was re instituted (67).

Mechanism of toxicity. Amiodarone-induced pulmonary toxicity appears to be related to the doses used because the majority of patients developing this complication have received amiodarone maintenance doses exceeding 400 to 600 mg/day (71). The mechanism of amiodarone-induced pulmonary toxicity has not been established. Changes may be related to the amphiphilic nature of the amiodarone molecule that contains both a highly apolar aromatic ring system and a polar side chain with a positively charged nitrogen atom. The drug may bind to phospholipids and inhibit their normal enzymatic degradation, resulting in their accumulation in lysosomes. The lung is a major site of phospholipid synthesis and turnover and would therefore be expected to show high concentrations of retained phospholipid (68,72,73).

Incidence. The frequency of pulmonary toxicity ranges from 0 to about 6%. Of 39 reported cases, 9 patients died and 30 had resolution of respiratory symptoms and radiologic abnormalities after withdrawal of amiodarone. Half of the patients who died and half of those who survived have been treated with steroids (67).

Thyroid Side Effects

Mechanism. Amiodarone has two atoms of iodine that compose 37% of the total molecular weight of the compound, or 75 mg of organic iodine/200 mg of active drug. About 10% of organic iodine may be deiodinated to yield free iodine, producing an amount that greatly exceeds the daily intake of iodine (0.5 to 1.0 mg) in the average American diet. Several features of the drug’s action on the heart resemble those produced by hypothyroidism and it is possible that the drug exerts part of its antiarrhythmic effect by selectively inhibiting the action of 3,5,3’-triiodothyronine (T3) on the myocardium by blocking the peripheral conversion of 3,5,3’,5’-tetraiodothyronine (T4) to T3 (74).

Amiodarone treatment results in significant elevations of T4 and reverse T3 with minor decreases in T3. Thyroid-stimulating hormone (TSH) levels may increase transiently but thyroid binding globulin remains unchanged (75,76). Serum reverse T3 levels may provide a basis for judging the magnitude of in vivo drug accumulation by correlating with the therapeutic response of the drug and the serious adverse effects. Reverse T3 has been reliable in one study (74) for monitoring the time course of the onset of drug action, the establishment of efficacy and the development of toxicity because an increase in reverse T3 occurs as a function of
drug dose and duration of therapy. There is no evidence to suggest that reverse T₃ exerts an antiarrhythmic effect nor that the toxicity of amiodarone is mediated by elevated levels of reversed T₃ (74).

**Clinical features.** Changes in thyroid function are not accounted by the iodine contained in the drug molecule because an amount of inorganic iodine equivalent to that found in amiodarone produces only slightly lower levels than normal of reverse T₃, T₄, and T₉ (75,76). Recovery of normal thyroid indexes after drug withdrawal is slow and may exceed 6 weeks. Despite the increase in total T₄, free T₄ and the free thyroxin index, heart rate is reduced by amiodarone in all patients.

Although the clinical changes in thyroid function are not the result of the iodine contained in the drug, it is possible that the development of clinically significant hypothyroidism or hyperthyroidism does result from the iodine contained in the drug and not from the direct pharmacologic actions of amiodarone (77,78). The frequency of amiodarone-induced thyrotoxicosis varies from 1 to 5% (79), but may be greater in patients with thyroid goiter induced by iodine deficiency. The determination of serum free T₃ levels and evaluation of clinical features based on medical history and physical examination are necessary to distinguish iodide-induced thyrotoxicosis from an alteration in the hormone metabolism in an otherwise euthyroid patient. Administration of thyrotropin-releasing hormone is useful because it fails to increase thyroid-stimulating hormone in patients with hypothyroidism. Development of thyrotoxicosis during amiodarone therapy may lead to the recrudescence of arrhythmia or angina that was present before initial therapy.

**Hypothyroidism** may occur in 1 to 2% of all patients treated with long-term amiodarone and results in a clinical picture indistinguishable from that of hypothyroidism due to other causes. Reverse T₃ and T₄ levels fail to increase during hypothyroidism; T₃ and T₄ concentrations decrease significantly while serum TSH levels increase.

**Conclusions**

Amiodarone is a unique antiarrhythmic agent, in part because of its interesting pharmacokinetics, wide range of efficacy and array of side effects. It appears to be one of the most effective antiarrhythmic drugs available today. Nevertheless, it is important that physicians be aware of amiodarone’s unique characteristics so that the drug is used properly in patients whose arrhythmias really require suppression. Most clinical experience with amiodarone in the United States relates to using this drug in high doses in patients with drug-resistant serious arrhythmias. It is quite possible that, when used in less difficult situations, lower doses and therefore fewer side effects might result.

**References**


