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Amiodarone: The Expanding Antiarrhythmic Role and How to Follow a Patient on Chronic Therapy

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Summary: Amiodarone was introduced as an antiarrhythmic compound in the early 1970s and was approved in the U.S. for the treatment of refractory ventricular arrhythmias in late 1984. Since that time the drug has become the most widely studied antiarrhythmic compound with expanding potential indications, including maintaining stability of sinus rhythm, secondary prevention in the survivors of myocardial infarction, and prolongation of survival in certain subsets of patients with congestive heart failure. Intravenous amiodarone was introduced in the U.S. in 1995 for the control of recurrent destabilizing ventricular tachycardia or ventricular fibrillation resistant to conventional therapy. The level of comfort in its use has risen considerably in the recent past. This has stemmed from the reasonably decisive evidence that class I agents increase mortality in patients with structural heart disease. In contrast, amiodarone either reduces mortality or its effect is neutral; this is consistent with its low to negligible proarrhythmic actions. The drug does not aggravate heart failure and it may even increase left ventricular ejection fraction and improve exercise capacity. Above all, it is becoming increasingly evident from wider experience and from controlled clinical trials that the side-effect profile of the drug is not as compelling an issue as it appeared to be when first used in much higher doses. Therefore, the overall objective of amiodarone therapy is to use the lowest dose that produces a defined therapeutic end point without causing serious side effects. Careful clinical surveillance in conjunction with monitoring of certain laboratory parameters and indices of efficacy at regular intervals permits the drug to be used effectively in a large number of patients who fail to respond to, or are intolerant of other antiarrhythmic compounds. Many experienced clinicians have begun to consider the use of amiodarone as first-line therapy in certain disorders of rhythm, especially in patients with severely compromised ventricular function.

Key words: class III antiarrhythmic drugs, ventricular tachycardia and fibrillation, sotalol, atrial fibrillation, heart failure, myocardial infarction, proarrhythmia, monitoring amiodarone therapy

Introduction

In recent years, probably no antiarrhythmic compound has generated as much clinical interest, and perhaps as much controversy, as amiodarone hydrochloride. The controversy centers on the combination of what appears to be an unparalleled efficacy and a complex array of side effects when it is used as an antiarrhythmic and antifibrillatory agent.[1] On both counts, it differs from other antiarrhythmic compounds. For this reason, it has been called the paradoxical agent,[2] and so it is. The efficacy of the drug and its variegated side-effect profile need to be interpreted within the framework of its pharmacodynamics and pharmacokinetics in the broadest sense and of experiential data with the extensive results from controlled clinical trials. An appreciation of the risk–benefit aspect of the drug allows the clinician to use it effectively in the lowest dose for a defined therapeutic end point relative to the lowest incidence of side effects as a function of time.

Pharmacodynamics and Electropharmacology

The complexity of the overall electropharmacologic profile of amiodarone is striking. The enigma of the drug's action continues to intrigue pharmacologists and cardiologists. Amiodarone lengthens repolarization but it is not just another class III agent. The compound exhibits all four electrophysiologic classes of action. Its sodium-channel blocking action is seen largely at fast heart rates and is not associated with the typical class I drug type of proarrhythmic effect; and unlike typical class I drugs, it does not increase mortality nor does it depress ventricular function. Rarely does it aggravate heart failure. Its class II or antiadrenergic actions resemble those of

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beta blockers without the typical beta-blocker side effects. Similarly, while it clearly lengthens the action potential duration as all other class III agents do, it differs from them in every other respect. Unlike all other class III agents, including sotalol, amiodarone does not exhibit rate- and use-dependency, that is, its action on repolarization is maintained over a wide range of frequencies. It reduces QT dispersion consistently and rarely produces torsade de pointes. The differences between the effects of intravenously and chronically administered amiodarone are shown in Table I. It is not well understood which electropharmacologic property or which aggregate of properties of this complex multifaceted compound are responsible for its desirable or undesirable actions in humans.

Pharmacokinetics and Approaches to Optimal Dosing

Pharmacokinetics

The clinical pharmacokinetics of amiodarone are not completely understood. The drug is highly lipophilic with long elimination half-life and is highly variable from patient to patient (35 to 110 days); it requires months for blood levels to reach equilibrium for optimal therapeutic effects. The oral bioavailability averages 30 to 50%, and excretion is minimal via the kidneys. The main pharmacokinetic indices of the drug are summarized in Table II. Amiodarone is metabolized in the liver producing several metabolites including desethylamiodarone (DEA), which has been identified during chronic therapy. DEA is pharmacologically active; it has an elimination half-life similar to that of the parent compound. Because of their high lipophilicity, amiodarone and its metabolites are extensively accumulated in liver, lung, fat, skin, and other tissues. Amiodarone doses need not be reduced in patients with renal disease. Amiodarone and DEA are not dialyzable. The ventricular myocardium develops a concentration 10 to 50 times that found in the plasma. The onset of action after intravenous drug administration generally occurs within several hours, whereas after oral administration the onset of action may require 2 to 3 days, often 1 to 3 weeks. Higher loading doses reduce this time interval but do not eliminate it.

There is reasonable linearity between plasma drug concentrations and amiodarone dosage, and the plasma level of the drug in patients successfully treated with amiodarone usually ranges between 1.5 and 2.5 μg/ml; DEA levels rise as a function of time and may either approximate those of the parent compound or exceed them. As a result, established pharmacokinetic principles do not provide a reliable basis for estimating or predicting the attainment of steady state with amiodarone. Nevertheless, patients receiving amiodarone prophylaxis for recurrent cardiac arrhythmias can be managed effectively if a rational approach to follow-up is adopted.

Proposed Dosing Schedules

Extensive experience has revealed a variety of dosing considerations that are of practical importance when using amiodarone. The most significant principle for maintenance therapy is to use the lowest dose of the drug that will produce the desired therapeutic effect without producing an intolerable or potentially serious side effect. The elimination half-life of amiodarone is unusually long, and the attainment of steady state in the individual patient is essentially empirical. Most in-

TABLE I Comparative electrophysiologic and pharmacodynamic properties of intravenous and chronic oral administration of amiodarone

Parameters	Intravenous amiodarone	Chronic oral amiodarone
Heart rate	±	Reduced +++
QT/QT_c intervals	±	Prolonged +++
QRS		
Slow rate	±	±
Fast rate	↑±	↑++
AV nodal conduction	↓±	↓++
Atrial ERP	↑±	↑+++
AV nodal ERP	↑++	↑+++
Ventricular ERP	↑±	↑+++
Bypass tract ERP	↑+	↑+++
Noncompetitive beta blockade	++	+++
Net antiadrenergic effect	++	+++
Negative inotropic effect	+	± (May be positive inotropic effect)
N-Desethylamiodarone	±	+++

Abbreviations: ERP = effective refractory period, ± = variable effect, + to +++ = graded effect from minimal to substanial, ↑ = increase, ↓ = decrease.

TABLE II Clinical pharmacokinetic profile of amiodarone

Absorption rate	T_{max}: 2–12 h (lab time 0.4–3h)
Extent of absorption	Poor and slow
Bioavailability	Variable (22–86%)
Protein binding	96.3 ± 0.6%
Volume of distribution	1.3–65.8 l/kg (acute)
Elimination	
Renal	Negligible renal excretion
Biotransformation	Hepatic and intestinal
Elimination half-life	3.2–20.7 h (acute)
	13.7–52.6 day (chronic)
Total body clearance	0.10–0.77 l/min
Pattern of elimination kinetics	First order
Metabolites	Major: mono N-desethylamiodarone
	Minor: bis-N-desethylamiodarone, deiodinated metabolites
Therapeutic serum	1.0–2.5 μg/ml range
Dose schedule[a]	Once daily
Special factors	Slow onset and offset of action

[a] For intravenous amiodarone see Table III and text for details.

vestigators have found that an initial loading dose of 800 to 1,200 mg/day (in two equally divided daily doses) for 1 to 2 weeks is usually adequate to produce close to a steady state in patients being treated for ventricular arrhythmias. For the control of ventricular tachycardia (VT) and fibrillation (VF), therapy is always initiated in hospital. In the past, higher doses for longer durations have been used; lower loading doses may be appropriate in patients with lower body weight, especially women. This regimen may be followed by an intermediate dose of 600 to 800 mg/day (in a single dose or two equally divided doses) for periods up to 2 to 3 weeks. At this stage, the dose may be reduced to 400 mg/day. Dose reduction may be necessary earlier in the event of side effects. For many patients, this dose will be sufficient for long-term maintenance during the first year, especially for those with ventricular arrhythmias. In some, the dose may be reduced even further (to 300–200 mg/day). In patients who are treated for ventricular arrhythmias, however, reducing the dose to 200 mg/day may result in a high risk of arrhythmia recurrence, particularly as a function of time. It should be emphasized that in the prophylaxis of supraventricular tachyarrhythmias (e.g., atrial fibrillation and flutter), both the loading and the maintenance doses can be much lower and therapy can be initiated safely in the outpatient clinic. Various regimens have been recommended. A reasonable loading dose is between 600 and 800 mg (in two divided doses) for a period up to 2 to 4 weeks; thereafter, it can be reduced to 400 mg/day and reduced further to 200 to 300 mg/day at 3 to 6 months in accordance with the clinical efficacy or the development of side effects. The usual maintenance dose for atrial fibrillation (AF) and flutter is 200 mg/day, although from time to time short periods of higher doses may be required in the event of breakthrough arrhythmias. In exceptional situations, satisfactory clinical efficacy can be obtained with 200 mg/day given 5 days of the week, especially in women of low body mass index.

As emphasized, dose reduction may be necessary at any time point in the loading or maintenance regimens if side effects occur. Nonetheless, dose adjustment at either phase is not reliably ascertained by the determination of serum levels of amiodarone, DEA, or reverse T_3, or by the magnitude of the QT interval on the 12-lead electrocardiogram (ECG), although all these indices have been used in the past. In the absence of side effects, the best approach appears to be the reliance on clinical indices of efficacy. There is increasing agreement that the so-called guided therapy in the case of VT and VF is not applicable to patients who are treated with amiodarone. A standardized dose regimen for intravenous amiodarone for the acute control of recurrent VT/VF is presented in Table III.

TABLE III Suggested dosage regimen of intravenous amiodarone for the suppression of recurrent destabilizing ventricular tachycardia and of ventricular fibrillation

Loading infusion		
Rapid infusion	1.5 mg/ml (150 mg in 100 ml D5W)	15 mg/min in 10 min
Followed by slow infusion		1.8 ml(900 mg in 500 ml D5W) 1 mg/min 33.3 ml/h over the next 6 h
Maintenance infusion	1 mg/ml	Reduce to 0.5 mg/min 16.6 ml/h over the remaining 18 h

For breakthrough arrhythmias, supplemental infusions (1.5 mg/ml–150 mg in 100 ml) may be given at a rate of 15 mg/min in 100 ml over 10 min. Alternatively, the rate of the infusions may be increased.

Antiarrhythmic Efficacy and Expanding Clinical Indications

In line with its electropharmacologic actions, amiodarone is a potent broad-spectrum antiarrhythmic agent.[1,3] It is highly effective in controlling ventricular and supraventricular arrhythmias in more than two-thirds of patients whose dysrhythmias have not responded to conventional agents. The major indications (formally approved, as well those not so) are listed in Table IV in which the major findings of practical and clinical importance are summarized. The salient issues with each category of disorder will be discussed in brief.

Ventricular Tachycardia and Fibrillation

Amiodarone exerts a potent suppressant effect over a wide spectrum of ventricular arrhythmias ranging from simple premature ventricular contractions (PVCs) to nonsustained and sustained symptomatic VT/VF. At steady state it is doubtful whether any other agent produces a similar degree of sustained arrhythmia suppression. The drug's particular value is in controlling VT/VF and in preventing recurrences of sudden death. It is effective in controlling malignant arrhythmias (including those with cardiac arrest) in 60 to 75% of cases in which conventional agents (especially class I compounds) fail or are not tolerated. Numerous large studies have confirmed its value in this setting.[4–6] The results from Weinberg *et al.*[6] are representative. They reported data from 469 patients who were treated with amiodarone and were followed for 5 years. The cumulative incidence of sudden death at 1, 2, and 5 years was 9, 13, and 22%, and for arrhythmia recurrence was 19, 26, and 28%, respectively. In this series only a small number of patients who had inducible sustained VT at control electrophysiologic study became noninducible during amiodarone therapy. The empirical use of amiodarone in VT/VF is further supported by the results of the CASCADE Study—Randomized Antiarrhythmic Drug Therapy in Survivors of Cardiac Arrest—a study that was undertaken to determine the comparative efficacy of guided therapy with conventional drugs (quinidine, procainamide, flecainide, or combination) to empirical therapy with amiodarone.[7] Although there is an increasing trend for the use of an implantable cardioverter defibrillator (ICD), it remains uncertain, at least for the present, whether drug therapy (especially amio-

TABLE IV Amiodarone: Established and potential expanding indications

Formulation	Arrhythmia (FDA status)	Efficacy
Intravenous	Refractory VT/VF (approved)	More effective than lidocaine, procainamide, and at least as effective as bretylium; less hypotension than bretylium
Oral	VT/VF (approved)	Superior to class I agents; can be given empirically; along with sotalol considered best medical therapy for VT/VF; studies (n = 3) comparing it with ICDs ongoing
	PVCs and NSVT	Powerful suppressant (may use in refractory symptomatic patients); impact on mortality unknown
	PSVT prophylaxis	Can be used in refractory cases when ablation is not available
	Atrial flutter	Prophylatic use when ablation not applicable or failed
	Atrial fibrillation	No placebo-controlled data, but appears to be the most powerful agent to maintain sinus rhythm long-term; slows ventricular rate on relapse; can be used in CHF; direct comparison with sotalol is needed; likely to become the most significant drug for long-term stability of sinus rhythm in AF
	Post-MI 2° prevention	Controlled (EMIAT and CAMIAT) and uncontrolled trials indicate reduction in arrhythmia mortality and trend in reduction in total mortality; meta-analyses of all trials indicate reduction in total mortality, sudden death, and cardiac mortality
	CHF	Two controlled trials (CHF STAT and GESICA)—somewhat divergent effect. GESICA: reduction in total mortality, CHF STAT: no effect; CHF STAT showed a strong trend for reduction in total mortality in nonischemic but not in ischemic cardiomyopathy; amiodarone increased left ventricular ejection fraction and may improve exercise capacity

Abbreviations: VT/VF = ventricular tachycardia and fibrillation; PVCs = premature ventricular contractions; NVST = nonsustained ventricular tachycardia; PVST = paroxysmal ventricular tachycardia; AF = atrial fibrillation; CHF = congestive heart failure. EMIAT, CAMIAT, GESICA, and CHF STAT are acronyms for clinical trials involving amiodarone. See text for more details.

darone or sotalol) for VT/VF is superior, inferior, or comparable to ICDs. This is a matter that remains unresolved[8–10] and is the subject of three ongoing randomized trials: (1) the Cardiac Arrest Survival in Hamburg (CASH), in which out-of-hospital cardiac arrest survivors are being randomized to ICD, amiodarone, and metoprolol;[11] (2) the Canadian Implantable Device Study (CIDS), in which patients with VT/VF are being randomized to empiric amiodarone or ICD;[12] and (3) the Antiarrhythmic Versus Implantable Device (AVID) study, in which patients with cardiac arrest or symptomatic VT are being randomized to best medical therapy (amiodarone or sotalol) versus ICD.[9] The results of these comparative drug and device trials are likely to be of far-reaching importance for the future management of patients with VT/VF and of survivors of cardiac arrest.

Intravenous Amiodarone in the Acute Control of Ventricular Tachycardia and Fibrillation

There have been numerous uncontrolled studies which suggested the potential of the drug for controlling refractory VT/VF without evidence of QT prolongation. A number of small and uncontrolled studies on the use of intravenous amiodarone in patients undergoing cardiopulmonary resuscitation (CPR) have also yielded promising results. Recently, the results of several controlled, blinded studies in patients with VT/VF on the effects of intravenous amiodarone in refractory VT/VF have been reported.[13,14] As summarized elsewhere,[15] two of the studies dealt with a dose-ranging trials in which patients with hemodynamically destabilizing VT/VF refractory to standard intravenous regimens of lidocaine and procainamide were randomized into three-limb parallel studies. In one of these, three doses of 500, 1000, and 2000 mg were infused over 24 h. In this study there was a clear trend toward a better response in the higher-dose groups in terms of event rate, but total and cardiac mortality were not statistically different among the groups. The study was not statistically powered to examine this issue. A greater degree of hypotension at the highest dose used was seen. In the second study, the three doses were 125, 500, and 1000 mg over 24 h. In this study there were more events per hour and a shorter time to first event in the low-dose group, and the differences among the groups were significant. In this study, the use of supplemental doses of the drug was permitted and it allowed the quantitation of the additional therapy as an end point. The third study was a double-blind comparison of two doses of amiodarone[14] 125 mg and 1000 mg, with intravenous bretylium (2500 mg/24 h) in patients refractory to procainamide and lidocaine. The higher-dose regimen of amiodarone had a comparable response to the group given bretylium, and both regimens were superior to low-dose amiodarone. Intolerable hypotension occurred twice as frequently with bretylium than with amiodarone requiring crossover to amiodarone. Other adverse reactions were minor, and there were no cases of tor-

sade de pointes in any of the study limbs. In the case of amiodarone, there was hypotension in 16% of the patients, but in less than 2% it was severe enough to require discontinuation of the drug. There was no significant difference in total or cardiac mortality among the three groups.

Thus, these results indicate that intravenous amiodarone may have a significant role in the acute control of recurrent refractory VT/VF when intravenous lidocaine and procainamide have been ineffective and bretylium has not been tolerated. A greater degree of hypotension was encountered with administration of bretylium than with amiodarone. The availability of intravenous amiodarone therefore provides an option to the clinician to follow up immediately or during the course of the infusion with the concomitant oral drug loading in an empirical fashion for the long-term prophylaxis against arrhythmia recurrence. In this respect, amiodarone has a clear advantage over lidocaine, procainamide, or bretylium which cannot be used in a similar manner. It should be emphasized that while the intravenous drug is undoubtedly effective in controlling VT/VF acutely, it remains uncertain whether intravenous loading of amiodarone shortens the period of loading by the oral route. However, the initial administration of the drug in patients who cannot take the oral drug (e.g., immediate postoperative patient with VT/VF), is an important therapeutic use of intravenous amiodarone. Uncontrolled data have suggested that intravenous amiodarone may be effective in facilitating the resuscitation of patients with cardiac arrest, but whether the drug should be added to the drug regimens being used during cardiopulmonary resuscitation is under consideration. However, it is noteworthy that the most recent ACC/AHA *Practice Guidelines for the Management of Patients with Acute Myocardial Infarction*[16] indicate an initial choice from one of the following intravenous regimens—lidocaine, procainamide, and amiodarone—for the control of sustained monomorphic VT not associated with angina, pulmonary edema, or hypotension, situations in which cardioversion will be preferable.

Amiodarone for Mortality Reduction in Patients at High Risk for Arrhythmic Death

There are subsets of patients with cardiac disease with accompanying electrical instability which may form the substrate for reduced survival from arrhythmic deaths. Such patients may have hypertrophic cardiomyopathy, recent or remote myocardial infarction, or congestive cardiac failure (CHF). In all three, there is increased frequency of occurrence of VT/VF. There are no controlled data in the case of hypertrophic cardiomyopathy and the data that are available are conflicting. Controlled but preliminary data are becoming available in the case of the post myocardial infarction (MI) patients and also in patients with cardiac failure.

Post Myocardial Infarction Survivors

Numerous clinical trials have established that beta blockers, aspirin, and angiotensin-converting enzyme inhibitors (ACEIs), as well as thrombolytic therapy when given prophylactically to the survivors of myocardial infarcts, do reduce mortality. Whether such an improvement might occur with amiodarone given prophylactically is a question that remains to be answered in a decisive manner. The early clinical trials have been nonblinded and not placebo-controlled; however, nearly all of them indicated favorable trends in mortality. Meta-analysis performed by Nademanee *et al.*[17] indicated reduction in sudden death, cardiovascular deaths, as well as in total deaths. An extensive meta-analysis of the entire data base dealing with mortality and sudden deaths under the influence of amiodarone (including those from EMIAT and CAMIAT—see below) is currently in progress.

Preliminary Results from Double-Blind Placebo-Controlled Trials

Two such trials have recently provided preliminary results. The first is the Canadian Amiodarone Myocardial Infarction Arrhythmia Trial (CAMIAT).[18] In the pilot phase of the CAMIAT, 77 survivors of infarction *who had arrhythmias* were randomized in a double-blind manner to either 300 to 400 mg/day amiodarone or placebo. One patient (1.2%) in the amiodarone group and 4 patients (13.8%) in the placebo group died as a result of arrhythmias, with an overall mortality of 10.4% and 20.7%, respectively. There was a trend in favor of amiodarone for all the major end points—arrhythmic deaths, resuscitated VF, and total mortality in the small pilot study. In the definitive study still to be published in full[19] and involving 1,250 patients enrolled with the criteria of recent myocardial infarction and with 10 PVCs/h, the primary hypothesis was that amiodarone will reduce arrhythmia mortality. The study was not powered to detect a significant change in total mortality. There was a 32.6% reduction in arrhythmia mortality ($p<0.001$), cardiovascular mortality was reduced by 27.6% ($p<0.01$), and all-cause mortality was reduced by 18.0%, which did not reach statistical significance. The European Myocardial Infarction Trial (EMIAT) focused on patients with left ventricular ejection fraction (LVEF) <40%,[20] perceived at being at a higher risk for sudden death than all consecutive cases of infarction taken as a group. EMIAT[21] was not a suppression trial, the primary end point being total mortality. Preliminary data reported at the 1996 Annual Scientific meeting of the American College of Cardiology (1996) indicated that amiodarone in the EMIAT did not reduce all-cause mortality. However, there were 50% fewer arrhythmic deaths in patients on amiodarone therapy compared with placebo and significantly fewer arrhythmic deaths plus resuscitated cardiac arrests in both EMIAT ($p<0.016$) and CAMIAT ($p<0.049$). It should be emphasized that these overall data (summarized in Fig. 1) from CAMIAT and EMIAT studies are new and in need of detailed scrutiny and interpretation. They need to be interpreted in the context of the entire body of evidence relating to the drug's effect on mortality in postinfarct patients as well as in other subsets of patients at risk for increased susceptibility to arrhythmic deaths. Such analyses may permit the delineation of the role

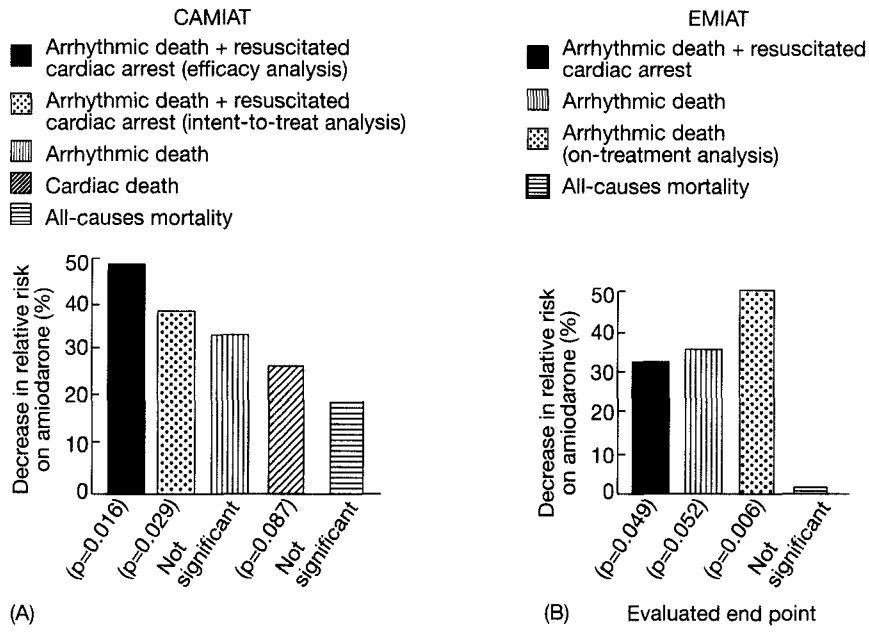

FIG. 1 Principal outcomes of the CAMIAT (A) and the EMIAT (B) studies with amiodarone in the survivors of acute myocardial infarction. Based on the data cited in Refs. No. 19 and No. 21. See text for details.

of amiodarone in the postinfarct patients for the purpose of mortality reduction over and above that achieved by standard current prophylactic therapy.

Amiodarone and the High-Risk Patient with Heart Failure

Two relatively large trials have been performed to examine whether prophylactic administration of amiodarone in patients with heart failure will lead to a reduction in total mortality and arrhythmic mortality. In a double-blind, placebo-controlled protocol sponsored by the VA Cooperative Studies,[22] 674 patients with congestive heart failure with >10 PVCs/h and LVEF ≤40% were randomized to placebo (n = 338) and to amiodarone (n = 336). At the median follow-up of 45 (0 to 54) months in this Congestive Heart Failure Survival Trial with Antiarrhythmic Therapy (CHF STAT),[22] there was no significant difference in all-cause mortality between placebo and amiodarone. There was also no significant difference between amiodarone and placebo in sudden death, but a trend in favor of amiodarone for reducing total mortality in patients with nonischemic cardiomyopathy ($p = 0.07$) except in those with ischemic cardiomyopathy. When the mortality data on the ischemic and nonischemic etiologies of heart failure were interpreted by including hospitalizations, there was a 46% reduction in the event rate[23] in the nonischemic patients compared with placebo ($p<0.01$). Amiodarone did also increase LVEF. The Argentinian study (Grupo de Estudio de la Sobrevida en la Insuficiencia Cardiaca en Argentina, or GESICA), in which 516 patients in New York Heart Association class III and IV CHF were randomized openly to amiodarone (300 mg/day) and to standardized medical therapy, revealed a significant reduction in mortality of the whole population.[24] There was a 28% reduction in all-cause mortality, from 41 to 36% ($p = 0.024$). GESICA and CHF STAT had markedly different numbers of patients with ischemic versus nonischemic cardiomyopathy. In GESICA, 39% of the patients had coronary artery disease compared with 72% in CHF STAT. These data provide a basis for further exploration of amiodarone in patients with nonischemic cardiomyopathy. Similarly, the marked increase in ventricular ejection fraction induced by amiodarone suggests that the role of the drug in improving exercise capacity and the quality of life of the patient with heart failure should be investigated systematically.

Amiodarone and Maintenance of Sinus Rhythm in Atrial Fibrillation

From the electrophysiologic standpoint, chronic amiodarone administration is likely to exert a potent antifibrillatory action in the atria in which it prolongs the action potential duration substantially.[25] In numerous albeit uncontrolled studies, it has been found to be the most effective drug in maintaining normal sinus rhythm. Middlekauff *et al.*[26] recently reviewed the results from relatively large, nonrandomized studies in which doses lower than those generally used for ventricular arrhythmias were given for AF. They found that low doses of amiodarone successfully maintained sinus rhythm in 53 to 79% of patients with paroxysmal or chronic AF during a mean follow-up of 15 to 27 months. Analysis of the world literature suggests that amiodarone maintains sinus rhythm in at least 65% of the patients given the drug after DC cardioversion. Most such patients were refractory cases who had failed on

multiple conventional antiarrhythmic compounds. In our own studies,[27] patients refractory to conventional therapy (mean number of drug trials 2.3 ± 1.4/patient, chronic AF in 44, paroxysmal AF in 47, mean age 59 years) were given a loading dose followed by maintenance doses of amiodarone (mean dose 277 + 102 mg/day). They were studied over a 10-year period, and the probability of their remaining in normal sinus rhythm (SR) was linear over 6 years. The actuarial rate of maintenance of sinus rhythm (after a month of loading) at 1, 2, and 5 years was 87, 80, and 57%, respectively. In 21 patients, arrhythmia recurrence necessitated amiodarone dose adjustment upwards after which 76% remained in SR at a mean follow-up of 2.3 years. The actuarial rate of drug discontinuation for side effects at 1, 2, and 5 years was 6, 12, and 27%, respectively, the most common being skin changes (5.5%), altered thyroid state (3.3%) or pulmonary fibrosis (3.3%), with no fatalities during the period of drug administration. There were no cases of torsade de pointes. It appears reasonable to assume that the drug withdrawal rate on low-dose (i.e., <400 mg/day) amiodarone is likely to be no more than 10% during the first year of therapy.

From these extensive studies, it appears that low-dose amiodarone is effective in maintaining SR in paroxysmal and chronic AF not only with a high success rate but also with an acceptable side-effect profile. However, while data for the effectiveness of amiodarone in patients with AF are compelling, blinded controlled studies are necessary to establish with confidence the role of the drug in the arrhythmia on the basis of indisputable data. Such studies involving placebo or sotalol are being initiated under the aegis of the Veterans Affairs Cooperative Studies Section.

Side-Effect Profile of Amiodarone

Amiodarone exhibits a wide array of side effects with a particular propensity to affect certain organs. In line with the drug's slow onset and offset of action, most side effects occur late, but some of those that affect the heart, the central nervous and the gastrointestinal systems can also occur during the loading phases of drug administration. The data on efficacy summarized here indicate that the observed beneficial effects of the compound should be balanced against the well-known and occasionally serious deleterious actions. It should also be emphasized that the overall incidence of adverse reactions to amiodarone in the U.S. has been declining over the last decade, compared with that of the previous decade during which the drug had been used in markedly higher doses. Despite this, there is no denying that the drug produces significant and distinctive side effects, but recent controlled and especially blinded studies have indicated that when the drug is given in a standardized manner in lower doses, the rate of overall side effects is relatively low. For example, in CHF STAT,[22] over a mean follow-up rate of 45 months and at a maintenance dose of the drug of 400 mg/day during the first year and 300 mg/day during the second and the subsequent years, the drug discontinuation was 23% on placebo and 28% on amiodarone (Fig. 2). This difference was not statistically significant.

Patterns of Amiodarone Side Effects

The bulk of the side effects caused by amiodarone are listed in Table V. Two phases of side effects with the drug should be recognized. The acute phase is dominated by the occurrence of changes in the gastrointestinal and central nervous systems and in the heart. All are reversible, as are the transient increases in the hepatic enzymes. During the chronic phases of drug therapy, a number of minor adverse reactions can occur and they are also reversible. Minor side effects include corneal microdeposits and subjective gastrointestinal side effects that seldom require drug discontinuation. Reports of macular degeneration have been uncommon. Amiodarone-induced hypothyroidism requires the addition of thyroid hormone replacement in about 5 to 8% of patients and possible discontinuation of the drug in about 2% of patients who develop hyperthyroidism. Neurologic side effects include peripheral neuropathy and myopathy. One recent study involving 151 patients given various antiarrhythmic drugs found that clinical abnormalities were present in a large number of patients taking antiarrhythmic drugs (flecainide, propafenone, amiodarone, and several with multiple drugs). The abnormalities were nonspecific, and amiodarone users did not appear to be at higher risk for polyneuropathy than subjects treated with the other antiarrhythmic drugs or even untreated patients with chronic disorders.[28] The precise incidence of hepatoxicity, thought to be 1%, is not known. More common are the transient increases in liver enzymes. Troublesome, increasingly common, but less serious side effects include mastalgia, epididymitis, and especially skin changes such as bluish skin pigmentation the incidence of which is unrelated to dose but increases as a function of duration of therapy. The major side effects that merit careful attention are pulmonary toxicity, altered thyroid abnormalities, and chronic skin pigmentation sometimes associated with skin atrophy.

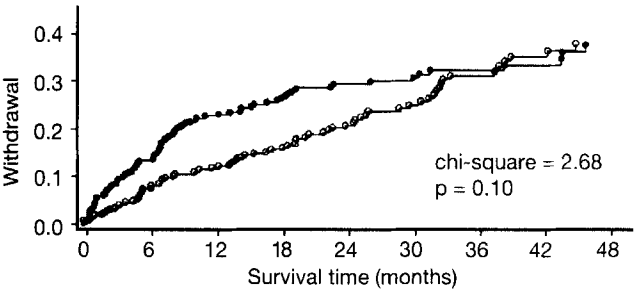

FIG. 2 Cumulative withdrawal rate of patients from placebo and amiodarone because of intolerable side effects in the CHF STAT trial.[22] The median follow-up was 45 months. Note that although a slightly greater number of patients withdrew from the amiodarone treatment limb compared with the placebo limb of the trial, the difference did not reach statistical significance over the course of the study. See text for further details. ••• = amiodarone, ○○○ = placebo.

TABLE V Side effects attributable to amiodarone therapy

Occuring early	
Gastrointestinal	Nausea, vomiting, constipation
Central nervous system	Headache, insomnia, impaired memory, hallucinations, ataxia
Cardiac	Bradycardia, sinus arrest, aggravation of arrhythmia (rare)
Occuring late	
Gastrointestinal	Constipation, nausea, weight loss (or sometimes weight gain)
Central nervous system	Headache, ataxia, hallucinations, impaired memory, peripheral neuropathy
Cardiac	Bradycardia, sinus arrest, atrioventricular block, torsade de pointes (rare)
Pulmonary	Pulmonary fibrosis with or without respiratory failure
Dermatologic	Photosensitivity, ecchymoses, pigmentation
Musculoskeletal	Proximal myopathy (rare)
Hematopoietic	Thrombocytopenia (rare)
Endocrinologic	Hyperthyroidism, hypothyroidism
Ophthalmologic	Corneal deposits; reduced visual acuity (rare), haloes, macular degeneration (uncommon)
Hepatic	Elevation of liver enzymes; hepatotoxicity (uncommon)
Miscellaneous	Gynecomastia; mastalgia; epididymitis

All adverse reactions shown are reversible, although rarely pulmonary fibrosis may prove fatal especially if diagnosed and treated late; death from hepatotoxicity, especially in the setting of preexisting liver disease, has been reported.

Pulmonary Toxicity

Pulmonary toxicity is a major concern in patients receiving amiodarone chronically. During the early years of therapy with amiodarone, the incidence of pulmonary toxicity was reported to be in the range of 5 to 15%. With much more stringent attention to dosage schedules, the incidence appears to have fallen to < 3% in many centers in the U.S.; it might be as low as 1% as noted in the Polish post-MI secondary prevention trial[29] and in the CHF STAT trial (1.2%). The lower incidence of pulmonary toxicity now encountered may be also be due to stricter criteria for the diagnosis of the complication by gallium scan and transbronchial lung biopsy. It should also be stressed that death due to pulmonary toxicity is now uncommon with increasing careful clinical surveillance of the patient and with the greater tendency to use lower doses. Although the initial experience with this drug had suggested that patients with underlying abnormalities of pulmonary function might be more susceptible to developing pulmonary fibrosis while taking amiodarone, this impression has not been borne out. In addition, it seems highly unlikely that serial monitoring of pulmonary function tests and chest x-ray studies (although recommended and widely used) might help early detection of this complication. The onset of pulmonary fibrosis tends to be relatively acute and 3-monthly or 6-monthly monitoring of pulmonary function tests or chest x-rays are unlikely to identify patients prone to developing pulmonary complications. Similarly, data are available to indicate that pulmonary toxicity can develop in patients who have serum levels of amiodarone in the so-called therapeutic range. During long-term follow-up, the most effective approach to reducing the incidence of pulmonary fibrosis appears to be clinical surveillance coupled with meticulous efforts to reduce the dose to the lowest level required to control the arrhythmia. Chest x-rays and other relevant investigations following the complaint of pulmonary symptoms are likely to identify the bulk of the patients liable to develop pulmonary fibrosis.

Thyroid Abnormalities

The development of abnormalities in thyroid state and in thyroid function tests is a major reason for regular measurement of thyroid function during chronic amiodarone therapy. A prudent approach is to perform these tests at baseline, then at 3- to 4-month intervals. After the first year, the frequency of monitoring may be reduced to twice per year. Changes are characterized by increases in T_4 and reverse T_3, with a modest reduction in T_3. No significant changes are seen in thyroid-stimulating hormone (TSH) except when hypothyroidism develops. Regular clinical and biochemical follow-up is essential because of the insidious development of hypothyroidism in approximately 2 to 10% of cases and hyperthyroidism in 1 to 5% of cases (the exact incidence varies by geographic location). The thyroid abnormalities are related to the presence of iodine in the amiodarone molecule. Clinically, one may suspect hypothyroidism from the appearance of marked bradycardia (as a result of combined effects of amiodarone and hypothyroidism), and markedly elevated TSH to approximately 20 units may occur without progression to clinical hypothyroidism. Such patients must be observed but not necessarily treated, especially those in whom the serum TSH is only twice the normal values (not exceeding 10 IU). Progressive increases in the level of TSH always requires treatment and clinical hypothyroidism usually supervenes. For such a complication, the drug need not be stopped and the patient responds well to thyroxine replacement therapy. In the case of hyperthyroidism, the earliest clinical indication may be an increase in heart rate from the bradycardic range (which

normally occurs with amiodarone therapy) and the reappearance of the arrhythmia, especially AF. This diagnosis is confirmed on the basis of clinical and biochemical findings. No systematic relationship is evident between the dose of the drug and the development of thyroid abnormalities. Once the diagnosis of hyperthyroidism is confirmed, it is prudent to discontinue amiodarone therapy and to treat the patient with an alternative antiarrhythmic regimen. If the altered thyroid state persists, conventional antithyroid therapy is indicated.

Skin Pigmentation

The complication of skin pigmentation cannot be readily correlated with the dose of amiodarone, but tends to develop in most patients as a function of the duration of therapy. The pigmented skin has a greater amount of amiodarone and its metabolite than does the nonpigmented skin. The recognition of a rapidly progressive change during a clinical follow-up is an indication for dose reduction or discontinuation of the drug.

Proarrhythmic Reactions and Conduction Abnormalities

An unexplained feature of the drug is the unexpectedly low incidence of torsade de pointes.[30] When torsade de pointes occurs in the setting of amiodarone therapy, it is usually (but not invariably) seen in conjunction with therapy with other QT-prolonging drugs such as quinidine or procainamide, or in the context of severe electrolyte disturbances. It remains puzzling that even in heart failure the incidence of torsade de pointes during chronic amiodarone therapy is low; there was not even a single case of the arrhythmia in the CHF STAT trial.[22] It should be emphasized that occasionally VT may be precipitated by amiodarone during the early loading phases of the drug and incessant arrhythmia has been described. These cases may be due to the initial class I actions of the drug which tend to resolve with the continued drug administration, presumably as the class III and antiadrenergic effects of the drug become dominant. Amiodarone may also produce significant and symptomatic bradycardia and sinoatrial block, especially in combination with rate-lowering calcium-channel blockers or beta blockers. In the case of sinoatrial block, pacemaker implantation may be required if drug therapy needs to be continued long-term.

How to Follow a Patient on Amiodarone Therapy

Baseline and Serial Measurements

In addition to clinical assessments, laboratory measurements should be obtained at baseline to aid in long-term surveillance. The laboratory data will enable the clinician to determine the significance of abnormalities known to develop during chronic amiodarone therapy—particularly drug-induced hepatic and lung toxicity, as well as hypo- or hyperthyroidism. The use of amiodarone is best avoided in patients with significant liver disease as well as in those known to have thyroid disorders. Routine baseline measurements are shown in Table VI. During chronic therapy, the tests listed in Table VII are repeated as often as deemed necessary on the basis of clinical findings. We no longer routinely perform slit-lamp assessments of the eye, nor do we perform serial lung function tests or chest x-ray studies, except when symptoms suggest lung toxicity.

Long-Term Follow-Up

We believe that every patient receiving amiodarone should be subjected to clinical evaluation at least once every 3 months during the early stages of therapy; once adequate efficacy has been attained, assessments may be performed less frequently (at 4- to 6-month intervals). The evaluation of continued efficacy in an individual patient on amiodarone is a matter of clinical judgment. The tests used to obtain objective data will vary with the arrhythmia being treated (Table IV). In the case of VT and VF, most clinicians now agree that guided therapy is not superior to the empiric administration of the drug.[31]

TABLE VI Routine baseline measurements in patients receiving amiodarone

Complete blood count
Serum electrolytes and serum creatinine
Liver function tests
Thyroid function tests
Serum digoxin or other drugs, the levels of which tend to increase during amiodarone therapy
Chest x-ray
Pulmonary function tests
12-lead electrocardiogram

TABLE VII Protocol for follow-up assessment of amiodarone patients

		Duration of therapy			Only with
Test	Baseline	3 mos	6 mos	12 mos	symptoms
Electrocardiogram	X	X	X	X	
Pulmonary function	X				X
Chest x-ray	X				X
Thyroid	X		X	X	
Liver enzymes	X		X	X	
Ophthalmic exam					X

The time intervals for clinical and laboratory monitoring may vary considerably relative to the complexity of the arrhythmias and the overall clinical condition of the patient.

TABLE VIII Pharmacokinetic interactions with amiodarone

Precipitant	Object drug	Consequences	Action
Amiodarone	Warfarin	Serum warfarin levels increase; prothrombin time increases; bleeding increases	Adjust dose of warfarin; may reduce by 50%
Amiodarone	Digoxin	Serum levels of digoxin increase; digoxin toxicity; gastrointestinal and central nervous system symptoms; cardiac effects—sinus arrest, atrioventricular block	Adjust dose of digoxin; reduce by half and periodically check serum levels
Amiodarone	IA drugs: quinidine, procainamide, disopyridamide; also NAPA (Class III)	Serum levels of these drugs may increase; QT interval may lengthen further and torsade de pointes may develop	Adjust dose and check serum levels
	IB drugs: aprindine, mexiletine	Serum levels of these drugs may increase, but clinical significance is unknown	Further data necessary
	IC drugs: propafenone, flecainide	Serum levels of these drugs may increase	Watch for electrophysiologic interaction
Amiodarone	Dilantin	Serum levels of diphenylhydantoin increase; dizziness, headache, diplopia, and other central nervous system symptoms may develop	May need to reduce dose of diphenylhydantoin

Significance of Serum Levels of Amiodarone and Desethylamiodarone

It should be emphasized that controversy currently exists regarding the use of serum levels of amiodarone and its metabolite to monitor the efficacy and toxicity of chronic therapy. Research has shown that most patients whose arrhythmias are successfully controlled have serum drug levels ranging from 1.0 to 2.5 μg/Ml, which has been considered the "therapeutic" range. Nonetheless, severe toxicity has been noted over this range, and the occurrence of most side effects does not bear a direct relationship to amiodarone levels. Present data do not, therefore, favor routine drug-level monitoring as a method to predict the efficacy or toxicity of acute or chronic therapy.[30]

Drug Interactions

A plethora of drugs exhibit either pharmacokinetic (Table VIII) or pharmacodynamic (Table IX) interactions with amiodarone. Close clinical surveillance is essential when patients are receiving concomitant therapy, and monitoring of serum levels may be important when persons are taking certain agents (for example, digoxin, quinidine, or procainamide). Amiodarone is unique in interacting with a number of other cardioactive agents which are metabolized in the liver. The list includes digoxin, warfarin, quinidine, procainamide, N-acetyl procainamide (NAPA), flecainide, propafenone, and phenytoin). Digoxin levels double and prothrombin times on warfarin may triple. Appropriate caution must therefore be exercised and concomitant usage of these drugs requires lower doses and close monitoring.

TABLE IX Pharmacodynamic interactions with amiodarone

Interactions	Consequences
Amiodarone and Class IA antiarrhythmic agents	Prolongation of QT interval; torsade de pointes; infranodal atrioventricular block
Amiodarone and beta blockers	Bradyarrhythmias; sinus arrest; atrioventricular block; sinoatrial block
Amiodarone and calcium antagonists (verapamil and ditiazem)	As with beta blockers
Amiodarone and hypokalemia	Prolongation of QT interval; torsade de pointes

Conclusions

Amiodarone is an unusual antiarrhythmic drug from the standpoint of its pharmacologic, electrophysiologic, pharmacokinetic, and hemodynamic actions. It does not depress ventricular function nor does it aggravate or induce heart failure except rarely. Its proarrhythmic effects are low and there are increasing data to indicate that, along with sotalol, it appears to be the most effective agent in the control of ventricular tachycardia and fibrillation. As far as total mortality is concerned, the drug's efficacy is comparable to that of implantable cardioverter defribrillators, and a number of controlled comparative trials are in progress. The new indication of

amiodarone is in the control of refractory destabilizing ventricular tachycardia and fibrillation in which the intravenous formulation is superior to intravenous lidocaine and procainamide; its effects are comparable to that of intravenous bretylium which, however, is less well tolerated. Another major use of the drug is likely to be in the maintenance of stability of sinus rhythm in patients with atrial fibrillation. Despite the recent accumulation of a wealth of data on this drug, dosing regimens must still be developed empirically and on an individualized basis. The monitoring of drug levels has not been of much value in optimizing efficacy and safety during short- or long-term therapy. Nevertheless, careful attention to the dose in relation to clinical observations and biochemical parameters will allow the clinician to use amiodarone safely and effectively in most patients. Significant toxicity can develop despite close monitoring, however, and alternative strategies will be needed in patients who exhibit such effects.

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