Toxic and Therapeutic Effects of Amiodarone in the Treatment of Cardiac Arrhythmias

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Amiodarone was used to treat cardiac arrhythmias that had been refractory to conventional medical therapy. The first 70 consecutive patients treated with amiodarone in this study had at least 6 months of follow-up (range 6 to 24, mean 11) and form the basis for this report. Sixty-six patients were treated for ventricular arrhythmias and four for supraventricular tachycardias.

Amiodarone therapy consisted of a loading dose of 600 mg orally twice a day for 7 days, and 600 mg daily thereafter. Doses were reduced only if side effects occurred. Because of frequent side effects, the dose was reduced from 572 ± 283 mg per day (mean ± standard deviation) at 45 days to 372 ± 174 mg per day at 6 months. With a mean follow-up of 11 months in the 54 patients who continued to take amiodarone, only 4 patients had ventricular fibrillation. Three additional patients experienced recurrent sustained ventricular tachycardia in long-term follow-up.

All 70 patients had extensive clinical and laboratory evaluation in follow-up. Side effects were common, occurring in 93% of patients. Thirteen patients (19%) had to discontinue the medication because of severe side effects. Fifty-six patients had gastrointestinal side effects, most commonly constipation. All patients but 1 eventually developed corneal microdeposits, and 43 patients were symptomatic. Cardiovascular side effects were uncommon. Symptomatic pulmonary side effects occurred in seven patients, with unequivocal pulmonary toxicity occurring in five. Neurologic side effects, most commonly tremor and ataxia, occurred in 52 patients. Thyroid dysfunction occurred in 3 patients, and 32 patients had cutaneous abnormalities. Miscellaneous other side effects occurred in 32 patients.

Amiodarone appears to be useful in the management of refractory arrhythmias. Because virtually all patients develop side effects when given a maintenance daily dose of 600 mg, lower maintenance doses should be used. It is unknown if the more severe side effects are dose-related. Amiodarone is difficult to administer because of its narrow toxic-therapeutic range and prolonged loading phase. More importantly, the first sign of antiarrhythmic failure may be manifest as sudden cardiac death.

Amiodarone is an investigational antiarrhythmic agent that has been recently introduced in the United States (1–4). It is a benzofuran derivative with weak alpha- and beta-adrenergic blocking effects and was originally tested as an antianginal drug. It was soon discovered that it had potent antiarrhythmic effects (5–10). Electrophysiologic properties of this agent consist of minor slowing of conduction, increase in action potential duration and refractoriness of atrial, ventricular and His-Purkinje tissue.

Amiodarone is considered to have little negative inotropic effect, and the occasional hypotension noted with the drug

has been attributed to peripheral vasodilation. One of the primary advantages of amiodarone is its long half-life, but a disadvantage of this same property is the long time required for the drug to exert its maximal antiarrhythmic effect (5).

Although amiodarone has been tested by many investigators and appears to be a good antiarrhythmic agent (11), its side effects have been reported to be infrequent (12,13). Corneal microdeposits appear in virtually all patients treated with the drug for long periods of time (14). Skin rashes are less common, but can include both photosensitive dermatitis and skin discoloration. Thyroid dysfunction (13,15) and pulmonary toxicity (16–19) have been reported, but have been uncommon. In addition, minor neurologic side effects have been noted (20). Side effects seem to correlate with dosage, but the proper dosage for treatment with amiodarone is unknown.

We report our experience with both the antiarrhythmic effects and the common side effects in our first 70 consecutive patients treated with amiodarone.

Methods

Patient population. Between August 1980 and December 1982, a total of 130 patients were started on amiodarone therapy because of symptomatic and refractory cardiac arrhythmias. All patients had failed to benefit from conventional antiarrhythmic agents (quinidine, procainamide, disopyramide and propranolol) either because of inefficacy or side effects. Inefficacy of conventional drugs was determined either by spontaneous recurrence of the clinical arrhythmia, ventricular tachycardia on Holter ambulatory electrocardiographic monitoring or electrophysiologic testing by programmed electrical stimulation. Some patients were not given disopyramide or propranolol because of preexisting severe congestive heart failure. Conventional drugs had been given in progressively increasing doses until side effects appeared or until the drugs were found to be ineffective at high therapeutic serum levels. Many patients had also been given other experimental antiarrhythmic agents, and conventional drugs had commonly been used in combination with other experimental agents (Table 1). Because of the reported length of time necessary for amiodarone to exert its full effect, it was commonly reserved as a last resort drug for use in patients who had failed therapy with other experimental antiarrhythmic agents that have a shorter half-life.

In the first 130 patients started on amiodarone, at least 6 months of follow-up were available on the first 70 consecutive patients treated with this drug. These 70 patients form the basis for this report. Mean follow-up for these 70 patients was 11 months (range 6 to 24).

Patients were referred for a variety of clinical arrhythmias (Table 2). They ranged in age from 32 to 78 years (average 59). There were 56 men and 14 women. Fifty of the 70 patients had clinical evidence of coronary artery disease; 21

Table 1. Previously Used Ineffective Drugs

	Patients	
	No.	%
Quinidine	69	99
Procainamide	70	100
Disopyramide	32	46
Propranolol	20	29
Phenytoin	5	7
Aprindine	17	24
Mexiletine	13	19
Tocainide	3	4
Clofilium	3	4
Bretylium	10	14

Table 2. Clinical Features of 70 Patients

Diagnoses	Patients (no)	
Clinical		
Coronary artery disease	50	
Cardiomyopathy	9	
Valvular disease	6	
Wolff-Parkinson-White syndrome	3	
Mitral valve prolapse	2	
Arrhythmia		
Ventricular fibrillation	32	
Single episode		25
Recurrent		7
With recurrent sustained ventricular tachycardia		16
Ventricular tachycardia	34	
Recurrent sustained		29
Recurrent unsustained		3
Single episode sustained		2
Supraventricular tachycardia	4	

patients had previously undergone coronary artery bypass graft surgery, 4 had experienced a cerebrovascular accident, and 10 had a history of chronic obstructive pulmonary disease.

All patients referred for refractory ventricular and supraventricular arrhythmias were considered for amiodarone therapy. All patients gave informed written consent to participate in this evaluation. The protocol was approved by the Human Subjects Committee at the University of Washington, beginning August 11, 1980.

Amiodarone protocol (Table 3). Patients were initially screened with a number of laboratory examinations before the institution of amiodarone therapy. Routine examination included history and physical examination, 12 lead electrocardiogram, chest X-ray examination, 24 hour ambulatory electrocardiographic (Holter) monitor, pulmonary function tests, thyroid function tests, radionuclide ventriculogram, slit lamp corneal examination, routine blood chemistry determinations and urinalysis and liver function tests.

Amiodarone therapy started with a dose of 600 mg orally twice a day administered for 7 days as an inpatient. The maintenance dose of amiodarone was then 600 mg daily thereafter. Because amiodarone requires such a long loading phase, patients were commonly left on the conventional antiarrhythmic drug that had been found to be the most efficacious in suppressing their arrhythmias to that time. That conventional drug was continued for 4 to 8 weeks after institution of amiodarone therapy, at which time the conventional drug was stopped to determine arrhythmia control with amiodarone alone.

Amiodarone dosage was decreased on the basis of side effects or increased if arrhythmias recurred after the initial 7 day loading phase (Fig. 1). Patients exhibiting good ar-

Table 3. Amiodarone Protocol

	Before Drug	1 Wk	Months									
			1	2	3	6	9	12	15	18	21	24
History	x	x	x	x	x	x	x	x	x	x	x	x
Physical examination	x	x	x	x	x	x	x	x	x	x	x	x
Electrocardiogram	x	x	x	x	x	x	x	x	x	x	x	x
Chest X-ray film	x					x		x		x		x
Holter monitor recording	x			x			x		x		x	
Slit lamp corneal examination	x			x	x							
Thyroid function tests	x			x			x		x		x	
Liver function tests	x				x							
Pulmonary function tests	x			x		x		x		x		x
Radionuclide ventriculogram	x			x								

rhythmia control without side effects were left on a 600 mg daily schedule. In patients exhibiting unequivocal side effects, the dose was decreased to 400 mg, then if necessary to 200 mg per day. Occasionally patients temporarily discontinued the drug and restarted it at a lower dose. Patients who had spontaneous recurrence of severe arrhythmias (ventricular tachycardia) in the first month after institution of therapy commonly had the dose increased transiently to 600 mg twice a day for another 7 days to 3 months, until arrhythmia control was obtained or side effects appeared.

After initial experience with the drug, during which time we noted elevations in serum quinidine and procainamide levels concomitant with the institution of amiodarone (21), patients routinely had daily determinations of serum levels of quinidine, procainamide and digoxin, if they were taking any of these medications, and prothrombin time if they were taking anticoagulants.

Follow-up examinations were performed frequently (Table 3). Patients were continuously monitored in the coronary

Figure 1. Amiodarone dosage versus time. Amiodarone was initially started at 1,200 mg orally daily, then reduced to 600 mg daily. The dose was reduced only if side effects appeared. Doses are depicted as mean ± standard deviation. Numbers at each value indicate number of patients.


AMIODARONE DOSING

care unit or in the telemetry unit until their arrhythmias appeared to be stable.

Spontaneous failures early in the course of therapy (within the first month) were not considered to be indications for a change in therapy. The drug was considered to be a failure only if arrhythmias recurred when severe subjective side effects limited an increase in dosage or if arrhythmias (such as sudden cardiac death or sustained ventricular tachycardia) recurred in the presence of moderate to heavy corneal microdeposits of amiodarone which suggested adequate total body stores of the drug.

Clinical follow-up. Antiarrhythmic effect was classified on the basis of the presence or absence of sudden cardiac death, sustained ventricular tachycardia requiring cardioversion, nonsustained ventricular tachycardia causing symptoms of syncope or presyncope and asymptomatic arrhythmias (including nonsustained ventricular tachycardia) as documented on Holter ambulatory electrocardiographic monitoring. Because most patients had received all conventional and many experimental antiarrhythmic agents, there was great pressure to continue amiodarone. Patients who stopped the drug usually had to return to combinations of previously unsuccessful antiarrhythmic agents or proceed to surgical therapy. Therefore, in general, any side effects that caused discontinuation of the drug were severe. Side effects were classified as mild if no dosage adjustment of amiodarone was necessary, moderate if the dose had to be lowered and severe if the drug had to be temporarily or permanently discontinued.

Electrophysiologic studies. Initially all patients had electrophysiologic testing before amiodarone administration. Patients were studied in the postabsorptive state, either nonsedated or lightly sedated with diazepam. One to four multielectrode catheters were inserted in the femoral and antecubital veins and positioned fluoroscopically (average skin dose of radiation = 1.2 rads). Lidocaine 1% local anesthesia was used, and lidocaine levels were measured at the time of stimulation. In no case was the lidocaine level in a therapeutic range. Patients were anticoagulated with
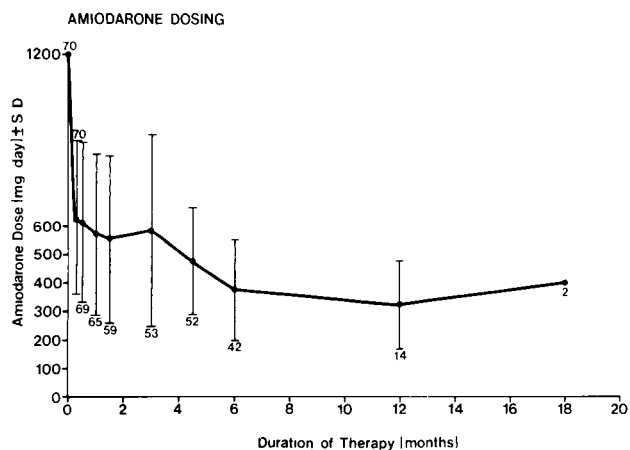
heparin. Right ventricular pacing was performed in at least two sites and at least three basic cycle lengths, usually 600, 500 and 450 ms. Single and double ventricular extrastimuli and burst pacing were used in an attempt to induce ventricular tachycardia.

The first patients in the series were tested only a few days or weeks after institution of amiodarone therapy before it was realized that a longer loading phase might be necessary for full drug effect. Subsequent patients were tested only after documentation of the presence of corneal microdeposits, usually 2 to 3 months after starting the therapy. One patient was studied less than 1 week after institution of therapy; 17 patients were studied 1 or more months, 13 patients 2 or more months and 8 patients 3 or more months after institution of therapy.

Ambulatory electrocardiographic monitoring. Holter monitoring was performed with two channel Oxford Medilog recorders and analyzed with a Reynolds Pathfinder II system. The system was interfaced with a Honeywell 1856-A fiberoptic recorder for continuous printout of all electrocardiographic complexes. All episodes of ventricular tachycardia were played in real time for further analysis. The technician has been documented to be 95% accurate using this system as compared with hand-counted tapes played in real time.

Arrhythmias were classified by severity, frequency and percentage of half-hour intervals containing each arrhythmia. Ventricular tachycardia was defined as three or more consecutive ventricular complexes at a rate of greater than 100 beats/min.

Electrocardiograms were evaluated in detail for the following variables: sinus rate, PR and QT intervals, QRS duration, presence of U waves and arrhythmia.

Radionuclide ventriculograms. Standard techniques were used for analysis of radionuclide ventriculograms. The radionuclide used was technetium-99m pertechnetate with stannous pyrophosphate-labeled red blood cells, 25 mCi per dose, yielding a dose of 0.42 rad (total body) and 1.38 rad (blood). These tests were analyzed for both right and left ventricular ejection fractions. Reproducibility of this technique in our laboratory of two left ventricular ejection fractions acquired and measured on the same day is ± 0.03 (standard deviation).

Pulmonary function tests. Pulmonary function tests were performed by standard techniques. Measurements routinely obtained were total lung capacity, diffusion capacity, forced vital capacity (FVC), residual volume, 1 second forced expiratory volume (FEV_1) and FEV_1/FVC. Reproducibility in the pulmonary function laboratory with these tests is ± 5% on the same patient on the same day and ± 15% on the same patient on different days. All tests were performed in the same laboratory to assure comparability of measurements.

Thyroid function tests. The following measurements of thyroid function were performed by standard methods: triiodothyronine (T_3) by resin uptake, thyroxine (T_4) by radioimmunoassay and thyroid stimulating hormone (TSH).

Slit lamp corneal examinations. Slit lamp corneal examinations were performed to assess amiodarone corneal microdeposition. Corneal microdeposits were classified as absent, faint, moderate or heavy. Examinations were performed at least at 2 months and every 6 months and commonly at more frequent intervals as clinically indicated.

Hepatic function tests. Standard serum tests for hepatic function included total bilirubin, glutamic oxaloacetic transaminase (SGOT), alkaline phosphatase, glutamic pyruvic transaminase (SGPT) and lactic dehydrogenase (LDH).

Antiarrhythmic drug levels. Amiodarone levels were unavailable at the time of the study. After it was recognized that there might be an interaction between amiodarone and other drugs, serum trough levels of the quinidine, procainamide and digoxin were measured every day for the first 3 days of amiodarone therapy and every other day thereafter as indicated. Serum levels of these drugs were analyzed by the standard radioimmunoassay methods. Likewise, prothrombin times were measured daily for all patients taking coumadin until it appeared that the prothrombin time was stable.

Statistical analysis. Data were compared using Student's t test for paired and unpaired data, chi-square analysis and Kaplan-Meier product limit estimates of survival as appropriate. Probability (p) values less than 0.05 were considered significant.

Results

Clinical antiarrhythmic efficacy. In a follow-up of 6 to 24 months (mean 11), recurrences of the sudden cardiac death syndrome or symptomatic sustained ventricular tachycardia requiring cardioversion were uncommon (Table 4).

Ventricular fibrillation. Three patients died of ventricular fibrillation, and another patient had ventricular fibrillation and was resuscitated successfully. One of these patients (Case 50) had been taking 400 mg of amiodarone daily for 2 months after the initial loading schedule. She remained asymptomatic, and slit lamp corneal examination at 2 weeks showed no deposits. Her ambulatory electrocardiogram continued to show multiform and paired ventricular premature beats but no ventricular tachycardia before the ventricular fibrillation. A second patient (Case 6) died in the hospital of ventricular fibrillation. She received the standard loading dose of 1,200 mg daily for 1 week and was then maintained on 600 mg daily. After 4 weeks, the dose was decreased to 400 mg daily because of severe constipation. Her episodes of ventricular fibrillation then recurred, and she died 3 months after starting the therapy. A third patient (Case 40) died suddenly after 9 months of taking 400 mg daily. Her ambulatory electrocardiogram continued to show nonsustained ventricular tachycardia. Higher doses of amiodarone were not tolerated because of constipation and skin rash. Another patient (Case 16) who had ventricular couplets

Table 4. Arrhythmia Recurrence on Amiodarone

| | | At Time of Arrhythmia | | Subsequent Course | | |
Case	Type of Arrhythmia	Dose/Day (mg)	Duration of Therapy (mo)	Dose/Day (mg)	Duration of Therapy (mo)	Arrhythmias
6	VF	400	3	—	—	—
40	VF	400	9	—	—	—
50	VF	400	2	—	—	—
64	VF, resus	1200	5 days	200	8	None
16	VT, sust→VF, resus	800	14	Surgery	2	None
18	VT, sust	600	14	Surgery	4	None
22	VT, sust	600	1.3	Surgery	4	None
56	VT, sust	400	5	800*	4	None
5	VT, nonsust— symptomatic	600	9	600†	15	None
46	VT, nonsust— symptomatic	900	3	Surgery	8	None
4	VT, nonsust— asymptomatic	400	19	400	5	None
20	VT, nonsust— asymptomatic	600	1.5	400	13	None

* Quinidine added to regimen. † Propranolol added to regimen.

Nonsust = nonsustained; resus = resuscitated; sust = sustained; VF = ventricular fibrillation; VT = ventricular tachycardia; — = patient died

on ambulatory monitoring developed sustained ventricular tachycardia, followed by ventricular fibrillation, from which he was resuscitated. An additional patient (Case 64) had ventricular fibrillation on the fifth day of amiodarone loading. He was successfully resuscitated, and amiodarone loading was continued. He was monitored for 3 additional weeks before hospital discharge, and has been well without recurrence of arrhythmias since then.

Sustained ventricular tachycardia. Three other patients have had a recurrence of sustained ventricular tachycardia. The arrhythmias were slow enough to be well tolerated hemodynamically but required electrical cardioversion. All of these patients had corneal microdeposits, and they had been on the drug for 5, 1.3 and 14 months at the time of their recurrence. One patient then had the dose increased from 400 to 800 mg daily and subsequently had quinidine readded to his regimen without further recurrence of his arrhythmias. The other two patients, who had been taking amiodarone, 600 and 800 mg/day, could not have the dose increased further. One of these two patients had postural hypotension and ataxia with a higher dose, and the other patient developed a peripheral neuropathy, proximal muscle weakness and abnormal liver function tests requiring termination of the therapy. Both of these latter two patients subsequently had surgery for their arrhythmias.

Nonsustained ventricular tachycardia. Four patients had recurrence of nonsustained ventricular tachycardia. Two of the patients were asymptomatic from this rhythm, but the other two patients had near syncopal episodes with their arrhythmias. One of the symptomatic patients (Case 5) could not have the dose increased further because of constipation and symptomatic corneal microdeposits. Propranolol was

added to this patient's regimen. The other symptomatic patient (Case 46) had neurologic side effects and postural hypotension at higher doses of amiodarone, so cardiac surgery was performed with electrophysiologically-directed aneurysm resection. Of the two patients who were asymptomatic from their nonsustained ventricular tachycardia, one patient could not have the dose of amiodarone further increased because of symptomatic heavy corneal microdeposits, and the other patient had to have his dose decreased because of worsening of pulmonary function tests suggesting early pulmonary toxicity. None of these four patients has had recurrence of nonsustained ventricular tachycardia, sustained ventricular tachycardia or sudden cardiac death.

Deaths from nonarrhythmic causes. Nine further patients have died of nonarrhythmic causes during follow-up while taking amiodarone. Patient 2 had further progression of his severe heart failure and died in cardiogenic shock 4 months after starting amiodarone therapy. His terminal admission was prompted by his decision not to take his diuretics, rapid accumulation of 20 pounds (kg) of edema fluid and electrolyte imbalance. His terminal rhythm in cardiogenic shock was a relatively slow ventricular tachycardia at a rate of 110 beats/min. Patient 3 likewise died of cardiogenic shock after slow progression of a low output syndrome 3 weeks after starting amiodarone therapy. He died with a slow idioventricular rhythm and even terminally did not have either ventricular tachycardia or ventricular fibrillation. Patient 7 also died from worsening congestive heart failure with an idioventricular rhythm as the terminal rhythm 2 months after starting amiodarone. Patient 8, who had suffered two previous myocardial infarctions without chest discomfort, developed worsening congestive heart failure

Table 5. Patients Who Discontinued Amiodarone Therapy Because of Side Effects

Case	Major Side Effects	Period Without Amiodarone Therapy (mo)	Spontaneous Arrhythmias Since Amiodarone Discontinuation
1	Myoclonus	24	VT, sust, multiple episodes
9	Agranulocytosis†	3	VF
11	Hemiballismus	20	None after surgery for VT/VF
12	Fatigue, memory loss	4	None
13	Wheezing*	9	VF
18	Neuropathy, thyroid dysfunction	5	None after surgery for VT
23	Thyroid dysfunction, skin rash	10	VT, sust, multiple episodes
25	Pulmonary toxicity	7	None
38	Pulmonary toxicity, neuropathy, thyroid dysfunction	3	None
52	Pulmonary toxicity	2	None
53	Headaches, fatigue	9	None
60	Tremors	9	None
62	Pulmonary toxicity	1	None

* Treatment terminated by patient, physicians did not attribute this symptom to amiodarone † Finding later determined not to be due to amiodarone.

Sust = sustained; VF = ventricular fibrillation, VT = ventricular tachycardia.

and abdominal pain 36 hours before death. The mechanism of his death is unknown, and an autopsy was not performed.

Patient 32 died of probable amiodarone pulmonary toxicity, though he also had a recent pulmonary embolus and myocardial infarction. Patient 42 died of progressive uncontrollable congestive heart failure. Patient 47 had severe hepatic disease before institution of amiodarone therapy. Even before amiodarone therapy, he had intermittent hepatic encephalopathy, but was also having recurrent ventricular fibrillation, unresponsive to conventional and other experimental antiarrhythmic agents. Three months after institution of amiodarone therapy, he died of hepatic encephalopathy. His arrhythmias had been controlled, but the dose had been progressively decreased, fearing that it worsened his hepatic function which was marginal even before the drug. Patient 48 died of a pulmonary embolus. Patient 58 died of progressive renal failure and electrolyte imbalance, which was thought to be unrelated to amiodarone.

Supraventricular tachycardia. Of four patients treated with amiodarone for supraventricular arrhythmias, the drug was discontinued in one (with recurrent atrial fibrillation) due to inefficacy, and in one (with Wolff-Parkinson-White syndrome and atrial fibrillation) because of side effects. Two other patients (both with Wolff-Parkinson-White syndrome) have continued therapy with good antiarrhythmic control.

Discontinuation of amiodarone because of toxic effects. Thirteen patients discontinued amiodarone because of side effects (Table 5). These patients were subsequently followed up for a mean of 8 months, and four of these patients had either ventricular fibrillation or sustained ventricular tachycardia after amiodarone was discontinued. These patients could be considered to be of a possible control group for the amiodarone patients because the medication was discontinued due to noncardiac side effects, not poor arrhythmia control. All of these patients were subsequently started on another therapy, 12 patients on the best alternate medical therapy and 1 patient on surgical therapy. This group with severe amiodarone toxicity consisted of 12 patients with ventricular arrhythmias and 1 patient with supraventricular arrhythmias. Of the patients with ventricular arrhythmias, there was a 33% incidence of sustained ventricular tachycardia or ventricular fibrillation (4 of 12) in 8.5 months, whereas after 1 week of loading therapy the amiodarone group had only a 13% (7 of 54) incidence of sustained ventricular tachycardia or ventricular fibrillation in 11 months (p = 0.009, Kaplan-Meier life table, Fig. 2). If only ventricular fibrillation after the first week of therapy is considered, 2 (17%) of the 12 patients who stopped amiodarone because of side effects had ventricular fibrillation in 8.5 months follow-up, whereas only 4 (7%) of the 54 patients who continued amiodarone had ventricular fibrillation in 11 months of follow-up (p = 0.2, Kaplan-Meier analysis, Fig. 3).

Electrophysiologic studies. In all patients ventricular tachycardia was inducible both before and after amiodarone, with an average cycle length of 269 before and 305 ms after amiodarone. In an additional two patients, ventricular tachycardia rapidly degenerated to ventricular fibrillation. After

Figure 2. Kaplan-Meier life table analysis of recurrence of sustained ventricular tachycardia (VT) or ventricular fibrillation (VF). Patients who continued amiodarone are compared with those patients who stopped amiodarone because of noncardiac side effects.
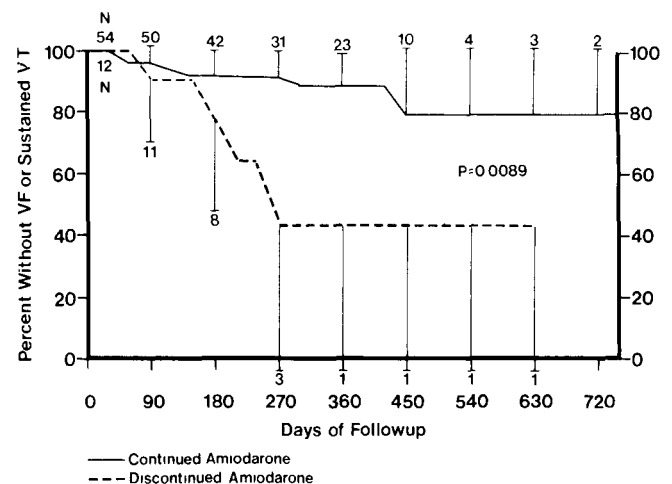
Figure 3. Kaplan-Meier life table analysis of recurrence of ventricular fibrillation (VF). Patients who continued amiodarone are compared with those patients who stopped amiodarone because of noncardiac side effects.
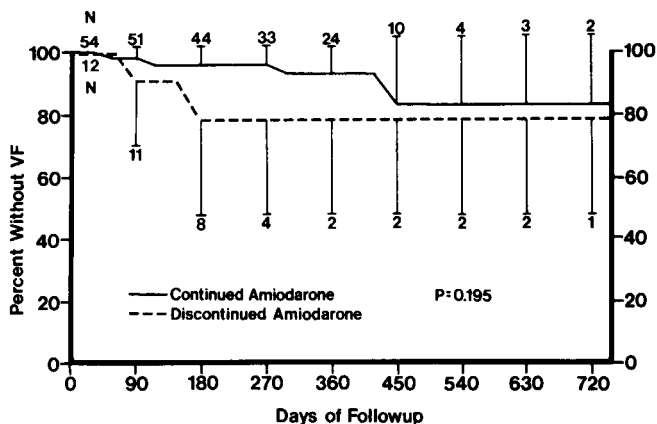
evaluation of these initial 18 patients on amiodarone alone, other reports appeared (22,23) suggesting that virtually all patients could still have ventricular tachycardia induced while taking amiodarone. Therefore, because our experience was confirmatory of these other reports, we elected to pursue evaluation of these patients more intensively by Holter ambulatory electrocardiographic monitoring.

Holter ambulatory electrocardiographic monitoring.

Because most of these patients were critically ill with ongoing malignant ventricular arrhythmias, the monitoring obtained before amiodarone therapy was always obtained while the patient was being treated with the best antiarrhythmic agent or combination thereof which had been beneficial in that patient before the use of amiodarone. Commonly these control recordings were also obtained on intravenous antiarrhythmic agents.

Number of premature ventricular complexes. Even though patients were taking other antiarrhythmic agents at the time of the control monitoring, the switch to amiodarone resulted in a trend toward a decrease in arrhythmia. Patients had a mean of $1,228 \pm 2,677$ premature ventricular complexes before and a mean of 238 ± 408 after amiodarone therapy $(0.05 < p < 0.10)$. Patients who subsequently had either ventricular fibrillation or sustained ventricular tachycardia in follow-up on amiodarone had a mean of 296 ± 538 premature ventricular complexes on the control Holter recording and 347 ± 477 on the follow-up recording (p = NS). Other patients who had no significant arrhythmias on follow-up (including those with nonsustained ventricular tachycardia) had $1,377 \pm 2,856$ premature ventricular complexes on the control Holter recording and 221 ± 404 on the amiodarone recording $(0.05 < p < 0.10)$. Though the patients who had no significant arrhythmias on follow-up had a higher density of premature ventricular complexes

before amiodarone administration, the difference was not statistically significant $(0.05 < p < 0.10)$. Therefore, it was difficult to tell which patients would do poorly on amiodarone on the basis of total counts of premature ventricular complexes.

Severity of arrhythmia. Likewise, classification of arrhythmia was not particularly helpful in determining which patients would do well and which would do poorly. Seven patients had ventricular tachycardia on the routine follow-up Holter recording. Three of these patients have been free of ventricular tachycardia, two patients have had either ventricular fibrillation or sustained ventricular tachycardia and two patients have had recurrence of nonsustained but asymptomatic ventricular tachycardia. Fifty patients have had no ventricular tachycardia on their amiodarone routine follow-up Holter recording while taking amiodarone: 45 of these have had no recurrence of symptomatic arrhythmias, 4 patients have had either ventricular fibrillation or sustained ventricular tachycardia and one patient has had recurrence of asymptomatic and nonsustained ventricular tachycardia. Of the six patients with either ventricular fibrillation or sustained ventricular tachycardia during follow-up, only two had ventricular tachycardia on their amiodarone follow-up Holter recording. Two other patients had no arrhythmias whatsoever; one patient had multiform premature ventricular complexes and couplets, and one patient had multiform single premature ventricular complexes. Of the three patients with nonsustained ventricular tachycardia in follow up, two had ventricular tachycardia on their routine follow-up Holter recording and one patient had only couplets. Three of the other 48 patients had ventricular tachycardia on the routine amiodarone follow-up Holter recording and all of these 48 patients have been free of arrhythmias, subsequently.

Therefore, from this small group of patients it is difficult to predict from the Holter monitor recording which patients will have significant arrhythmias on follow-up. There is a weak trend suggesting that patients who have high density premature ventricular complexes on the control Holter recording and who exhibit a dramatic decrease in the premature ventricular complex counts will do better, whereas those patients who have fewer premature ventricular complexes on control Holter recording and who actually have an increase in their premature ventricular complex counts will do worse.

Electrocardiographic effects. Amiodarone commonly changed the electrocardiogram in a characteristic manner (Table 6). Heart rate decreased, PR interval lengthened, QRS interval lengthened, QT interval lengthened and large U waves commonly appeared. Though patients were usually taking other antiarrhythmic drugs at the time of the control electrocardiogram that alone would tend to lengthen the electrocardiographic intervals, these drugs were commonly discontinued in the early months of amiodarone therapy. Cessation of these other antiarrhythmic drugs would have

Table 6. Electrocardiographic Effects of Amiodarone

	Before Amiodarone	After Amiodarone*	p
Heart rate (beats/min)	72 ± 12	65 ± 11	< 0 001
PR interval(s)	0.19 ± 0.03	0.21 ± 0.04	< 0 001
QRS duration(s)	0.11 ± 0.003	0.12 ± 0.04	< 0.005
QT interval(s)	0.43 ± 0.06	0.46 ± 0.07	< 0 001

* 2 to 6 months after initiation of amiodarone therapy

p = probability.

tended to shorten the sinus interval, QRS duration and PR and QT intervals.

The decrease in heart rate due to amiodarone was not symptomatic in any patient, although some patients developed a heart rate of less than 50 beats/min. One patient had preexisting profound sinus bradycardia with rates as low as 30 beats/min, and the patient's chronic fatigue was treated with a permanent pacemaker. However, amiodarone did not worsen her preexisting sinus bradycardia or congestive heart failure. Another patient had profound sinus bradycardia with junctional escape rhythms. His junctional rate was commonly in the 40s, and amiodarone reduced his heart rate to the low 40s or upper 30s. In addition, his heart rate was less responsive to exercise than it had been before amiodarone therapy. Two other patients developed mild sinus bradycardia with heart rates unresponsive to exercise.

Effects on ventricular function. Radionuclide left ventricular ejection fraction averaged 0.40 ± 0.14 before amiodarone therapy; the minimal value was 0.10 and the maximal was 0.87. After 6 to 12 weeks of amiodarone therapy, the minimal left ventricular ejection fraction was 0.12, maximal 0.86 and the mean 0.41 ± 0.16. This change in ejection fraction was not significant (n = 57, paired *t* test). The majority of the other 13 patients not included in this paired analysis had amiodarone discontinued or died before it was time for the follow-up determination of left ventricular ejection fraction.

Right ventricular ejection fraction was less commonly determined, being measured before and after amiodarone in 30 patients. The mean right ventricular ejection fraction was 0.39 ± 0.14 before and 0.39 ± 0.13 after amiodarone therapy. The maximal and minimal right ventricular ejection fractions were 0.92 before and 0.15 and 0.64 and 0.16 after amiodarone, respectively.

Clinical congestive heart failure. Though the mean left ventricular and right ventricular ejection fractions were unchanged, nine patients continued to have clinical deterioration of left ventricular function during amiodarone therapy. Six of these nine patients had New York Heart Association (NYHA) functional class III congestive heart failure and 3 had class II heart failure before institution of amiodarone. At some time during the therapy, the dose of amiodarone was reduced in all nine patients because of the fear that the drug had contributed to the worsening of left ventricular function. It is uncertain whether amiodarone precipitated worsening of congestive heart failure or if these patients were simply manifesting progression of their intrinsic disease. Changes in ejection fraction in individual patients could not be explained by the duration of amiodarone therapy or dose of amiodarone.

Thus, congestive heart failure was new or worse in 9 of the 65 patients in whom left ventricular ejection fraction was measured before amiodarone therapy. If the initial left ventricular ejection fraction was 0.35 or less, 7 patients had new or worse congestive heart failure and 23 patients remained unchanged. If the initial left ventricular ejection fraction was more than 0.35, 2 patients had worsening or new congestive heart failure, and 33 patients were unchanged (p < 0.05).

Postural hypotension. Two patients developed some postural hypotension when amiodarone was combined with either quinidine or procainamide, and the blood pressure returned to normal when either quinidine or procainamide was discontinued.

Therefore, it appears that amiodarone does not consistently change left ventricular ejection fraction, though the risk of new or worsening congestive heart failure is greater in patients whose initial left ventricular ejection fraction is 0.35 or less.

Pulmonary complications. Pulmonary function tests in this entire group of patients were unchanged. Total lung capacity decreased only from 97 ± 20 to 94 ± 19% of predicted; diffusion capacity decreased from 93 ± 25 to 88 ± 30% of predicted and FEV$_1$/FVC increased from 76 ± 10 to 78 ± 9% of predicted. However, none of these changes reached statistical significance. These pulmonary function tests were performed a mean of 5.6 ± 3.2 months after initiation of amiodarone therapy. No other changes were made in other medications known to affect pulmonary performance, and all but one patient had evidence of corneal microdeposits by slit lamp examination at the time of the follow-up measurements. Patients were taking a mean dose of 7.2 ± 2.4 mg/kg body weight.

Syndrome of amiodarone pulmonary toxicity. This syndrome is poorly defined. It has usually been characterized as a constellation of cough, dyspnea on exertion, fever, infiltrates on chest X-ray examination and decreased diffusion capacity and total lung capacity. It has been described as a restrictive process, with pathologic features of pulmonary fibrosis. However, it is not entirely a restrictive process, and it can occur acutely.

In our 70 patients, there were five patients with unequivocal amiodarone pulmonary toxicity and another six patients who had possible amiodarone pulmonary toxicity (Table 7). These complications occurred between 3 and 13 months of the initiation of therapy without much warning.

Table 7. Amiodarone Pulmonary Toxicity

	Amiodarone Therapy		Preamiodarone		
Case	Dose (mg/kg)	Duration (mo)	DLCO	TLC	Chest X-ray Film*
Patients With Definite Toxicity					
25	6.7	3	77	98	1+
32	8.5	13	110	68	0
37	8.5	12	70	96	1+
52	9.4	8	70	110	1+
62	15.6	7	72	93	1+
Patients With Possible Toxicity					
20	10.4	9	80	106	1+
22	7 5	6	79	109	1+
34	12.0	9	127	107	0
35	5 4	6	77	77	0
38	5.9	9	48	78	1+
69	5.5	5	92	100	0

* Degree of interstitial changes on baseline chest X-ray film, graded 0, 1+, 2+, 3+ and 4+
DLCO = pulmonary diffusion capacity, TLC = total lung capacity

The syndrome in these five patients was characterized by abrupt appearance of cough and dyspnea on exertion associated with new pulmonary infiltrates and diffuse rales. Patients were often treated either for pulmonary edema or viral or bacterial infection at other hospitals before it was recognized that these changes were probably due to the amiodarone. The pulmonary infiltrates were commonly peripheral, involving the lower lung fields. It was difficult to distinguish between pulmonary infection, pulmonary edema and amiodarone toxicity, and it was often the subsequent course that confirmed the diagnosis: lack of sputum production, negative cultures, lack of response to antibiotics and low pulmonary capillary wedge pressure.

One patient (Case 32) in this group of 70 patients died 5 days after presentation with worsening dyspnea. He experienced significant congestive heart failure before this time, and it was thought that many of his symptoms could be attributed to his congestive heart failure. However, diuresis of 2.7 kg of fluid did not improve his dyspnea, and the chest roentgenogram showed progressive worsening during this time. Pulmonary capillary wedge pressure was 6 mm Hg, and the patient subsequently died when adequate oxygenation could not be maintained. On postmortem examination he had a huge heart, congested lungs, evidence of multiple small pulmonary emboli, a new occlusion of a small branch of the right coronary artery, pulmonary changes of alveolar septal thickening and proliferation of alveolar clear cells filling the air spaces.

Amiodarone pulmonary toxicity occurred either early or late in patients taking as little as a 200 mg daily maintenance dose, although two patients were taking 600 mg daily, and two patients were taking 800 mg daily. However, there were some clues to predict which patients would develop toxicity.

Pulmonary function tests showed that the baseline diffusion capacity was lower (80 ± 17%) prior to the drug in the group with certain pulmonary toxicity than in the remaining patients (98 ± 26%). If the baseline diffusion capacity was 80% or less of predicted, 47% of these patients had worsening of chest X-ray findings, and 25% of patients had worsening symptoms. For those patients whose baseline diffusion capacity was greater than 80% of predicted, only 6% had worsening of chest X-ray findings and 11% had worsening sypmtoms.

In our larger series of all of the first 130 consecutive patients (which includes the first 70 patients reported here in detail), there were seven certain cases of pulmonary toxicity and six possible cases. The two additional cases of certain pulmonary toxicity in the second series of 60 patients were observed in patients who had been taking 7.5 and 8.5 mg/kg, respectively, amiodarone maintenance dose daily. They had been treated with the drug for 2 and 3 months, respectively. Initial diffusion capacity was below 80% in both, 79% in one and 70% in the other. One of these two patients died. He presented with what appeared to be pulmonary edema that did not clear with vigorous diuresis. After diuresis, there were peripheral lower lung field infiltrates on X-ray examination persisting for weeks with diffuse rales. Amiodarone therapy was stopped. Recurrent ventricular tachycardia had returned approximately 6 weeks after the amiodarone had been stopped, and 2 weeks later the patient died of progressive congestive heart failure as he was being treated with other antiarrhythmic agents. On postmortem examination he likewise had alveolar septal and interstitial thickening compatible with pulmonary fibrosis due to amiodarone. In addition, he had diffuse proliferation of alveolar cells obliterating many of the air spaces.

Table 8. Thyroid Function Tests

	Before Amiodarone	After Amiodarone							
		1 Mo	p	3 Mo	p	9 Mo	p	Last Value*	p
T_4 (4.1 to 11.3 µg%†)	7.0 ± 1.7	8.8 ± 2.3	< 0.001	8.4 ± 3.0	< 0.02	8.5 ± 3.0	< 0.02	8.6 ± 2.5	< 0.001
T_3 (33 to 45%†)	42 ± 6	40 ± 6	NS	40 ± 6	NS	39 ± 6	< 0.05	40 ± 6	NS
TSH (< 6.5 µU/ml*)	7.4 ± 8.7	13.1 ± 17.5	NS	21.5 ± 36.9	< 0.025	18.8 ± 26.3	< 0.05	13.8 ± 19.0	< 0.025

* Final determination in follow-up. † Normal value.

NS = not significant; p = probability value compared with data obtained before amiodarone; T_4 = thyroxine measured by radioimmunoassay; T_3 = triiodothyronine measured by resin uptake; TSH = thyroid stimulating hormone.

In all patients who had definite or suspected pulmonary toxicity, amiodarone administration was at least transiently discontinued. In one patient, amiodarone was reinstituted at 100 mg daily 2 months later when his evidence for pulmonary toxicity had disappeared and arrhythmias began to recur. This patient remains on that dose, free of arrhythmias and free of evidence of recurrence of pulmonary toxicity for 2 months.

Thyroid function. Table 8 summarizes the effect of long-term amiodarone therapy on thyroid function. Before amiodarone, serum thyroxine (T_4) was 7.0 ± 1.7 µg%, increasing consistently in most patients by 1 month of therapy and remaining elevated. The serum triiodothyronine (T_3) at control was normal and decreased slightly, significant only at 9 months. The thyroid stimulating hormone was slightly elevated in the group as a whole before amiodarone, and it increased progressively throughout the duration of therapy. It is common that this hormone is slightly elevated in patients with severe debilitating disease, but it increased dramatically in some patients, greater than 100 µU/ml in three patients.

Clinically evident hypothyroidism was seen in only three patients, with some symptoms questionably related to hypothyroidism in an additional three patients. No patients developed clinically evident hyperthyroidism.

Corneal microdeposits. Figure 4 illustrates the percentage of patients whose slit lamp examinations were positive at various times during follow-up. Almost all patients eventually develop corneal microdeposits, with the majority of patients having deposits visible between the second and third months. The earliest deposits were seen at 5 weeks, and the only patient who did not develop corneal microdeposits on long-term follow-up was also the only patient in the series who wore contact lenses. Ocular side effects were common, but mild. Patients most frequently complained of halos visible around bright lights at night, and some patients also complained of a gritty sensation in the eyes or itching, dryness or photophobia.

Hepatic function tests. Though there was a trend toward elevation of serum enzymes, the variability from patient to patient was quite dramatic, and there were no sta-

tistically significant differences between values before or after amiodarone therapy. Serum bilirubin was unchanged: 0.5 ± 0.3 mg% before and 0.6 ± 0.4 mg% after amiodarone. Serum alkaline phosphatase rose only from 82 ± 36 to 99 ± 57 U/liter. SGOT rose from 22 ± 13 to 93 ± 391 U/liter, but the standard deviation was large enough that this value did not reach statistical significance at the p < 0.05 level. SGPT increased from 26 ± 20 to 36 ± 21 U/liter, and LDH increased from 227 ± 80 to 353 ± 342 U/liter. Many of the baseline hepatic function values were elevated, perhaps in some cases because patients were undergoing repeated DC cardioversion and resuscitation immediately before the initiation of amiodarone.

No patient developed clinically significant hepatic dysfunction. One patient who started with hepatic precoma exhibited further deterioration of his hepatic function over the course of therapy. It is uncertain whether this deterioration was secondary to the natural course of his disease or

Figure 4. Percent of patients with corneal microdeposits versus time. Most patients had deposits at 3 months.

AMIODARONE
CORNEAL MICRODEPOSITS
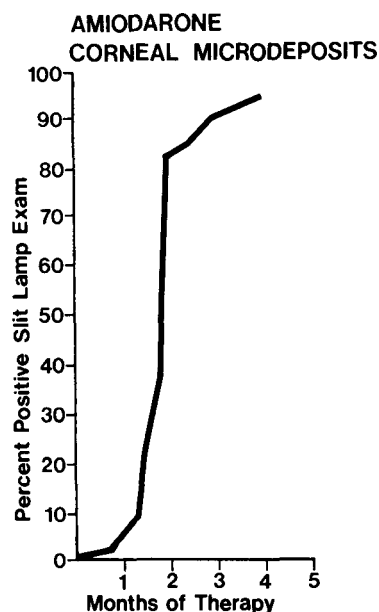
the amiodarone. His initial bilirubin was 1.6 mg%, increasing to 2.9 mg% after 2 months of therapy. Alkaline phosphatase was 185 U/liter, increasing to 278 U/liter after therapy. SGOT increased from 24 to 32 U/liter, and SGPT was unchanged at 24 U/liter before and 22 U/liter after amiodarone.

Drug interactions. Concomitant administration of other cardiac drugs was common in patients treated with amiodarone. Because many patients were having on-going arrhythmias, conventional antiarrhythmic agents were usually continued during the amiodarone loading phase to provide at least an element of antiarrhythmic protection. We found interactions with a number of other cardiac drugs, as reported elsewhere by us (21) and by other investigators (24–30). We found that amiodarone decreases dosage requirements for digitalis, quinidine, procainamide and Coumadin (Table 9).

Only one patient whose digitalis levels were elevated developed symptoms and signs of toxicity which included nausea, vomiting and bradycardia. Though patients commonly demonstrated electrocardiographic manifestations of elevated quinidine or procainamide levels (widened QRS complexes, long QT intervals or bradycardia), only five patients developed symptoms of quinidine toxicity and one developed symptoms of procainamide toxicity. No bleeding occurred with prolongation of prothrombin time, but dosages of Coumadin were adjusted promptly.

Subjective side effects. Table 10 outlines the subjective side effects experienced by patients, classified as mild, moderate or severe. Most common subjective side effects were related to the gastrointestinal tract. Constipation or obstipation occurred in 39 patients. Seven patients had nausea, five had anorexia and five had ageusia.

Neurologic symptoms most commonly consisted of tremor (17 patients), ataxia (11 patients) and dizziness (8 patients). At times these symptoms were devastating, requiring termination of the drug. A few patients experienced a variety of other neurologic side effects including memory loss, vertigo, headache, myoclonus, hemiballismus and peripheral neuropathy.

Cutaneous manifestations were seen in 32 patients, which usually consisted of photosensitivity or itching. Patients

commonly had to use a sunscreen to prevent sunburn, and some patients described a "crawling" or "prickling" sensation beneath the skin. One patient developed hyperkeratoses, and another two patients were aware of a dark blue skin discoloration. A milder slate blue discoloration was evident to physicians in two additional patients, but it was not noticed by the patients or their families.

Other subjective side effects included epididymitis in seven patients, requiring temporary discontinuation of amiodarone in four patients and subsequent dose reduction in all.

Thus, of the 70 patients reported in this series, 65 patients had subjective side effects. Only one patient in the entire series has both continued to take amiodarone without ever developing any subjective side effects and has remained free of arrhythmias.

Discussion

The ideal antiarrhythmic agent is still unavailable. An ideal agent should be efficacious, well tolerated with few side effects, have a long half-life and infrequent dosing intervals, a high therapeutic to toxic ratio, should not affect other organ systems or be affected by diseases of other organ systems and should be relatively inexpensive. Amiodarone fails these strict criteria because of its frequent side effects.

Dosage of amiodarone. Side effects of amiodarone, given according to the dosage schedule outlined, are almost universal but fortunately often minor. At the time that this study was initiated, recommendations for amiodarone dosage were generally larger than recommendations made today (31,32), and it is possible that many of the side effects could be avoided by using lower doses of the drug. However, choosing the proper dose of this drug is difficult. The lowest possible dose should be used to attempt to limit side effects, but on the other hand, the dose should be kept high enough for optimal arrhythmia control. In patients with severe ventricular arrhythmias, the first evidence for an inadequate dose can be the appearance of sudden cardiac death. Even with the relatively large maintenance dose used in this study (with its attendant side effects) there were six recurrences of ventricular fibrillation and five recurrences of sustained ventricular tachycardia in the total group (including those patients who stopped the drug).

A major limitation of amiodarone is the time required for the drug to become effective. One study (5) reported that the antiarrhythmic effect appeared at approximately 9 days. Patients with recurrent, life-threatening ventricular arrhythmias need control more quickly, and it is possible that the full effect of amiodarone cannot be obtained for 1 to 2 months after the drug therapy has been started. Some authors (33) suggest that this problem may be obviated by starting with the intravenous drug. Patients in our series had to remain in the hospital on a cardiac monitor until we were

Table 9. Drug Interactions With Amiodarone

Drug	No. Patients	% Increase in Serum Level*	% Dose Reduction Required†
Digitalis	4	280	50
Quinidine	11	32	37
Procainamide	12	57	20
Coumadin	11	–	43

* At constant drug dose. † To maintain constant serum level.

Table 10. Amiodarone Side Effects

	Mild			Moderate			Severe		
	+	±	−	+	±	−	+	±	−
Gastrointestinal									
Constipation	33			4			1		
Obstipation							1		
Nausea	1	1		3	1		1		
Anorexia	1	1		1			2		
Ageusia	2	1		2					
Ocular									
Halo effect	17								
Blurred vision	5		1						
Eye itching, dryness	10			1					
Photophobia	8			1					
Cardiovascular									
Postural hypotension		1		1	1				
Bradycardia	2			3					
Worsening CHF		1			6			2	
Pulmonary									
Dyspnea on exertion with pulmonary infiltrates							7		
Neurologic									
Headache		1					1		
Dizziness	1	3		3			1		
Ataxia	4			5			2		
Vertigo	1			3					
Short-term memory loss	2			2			2		
Myoclonus—abdominal							1		
Tremor	14	1		1			1		1
Hemiballismus							1		
Paresthesias—peripheral neuropathy							1		
Endocrine									
Hypothyroidism	2	1		2			1		
Parotid swelling							1		
Cutaneous									
Photosensitivity	16			1					
with rash	7								
Change in skin color	2								
Hyperkeratoses							1		
Itching	3			2					
Miscellaneous									
Interrupted sleep pattern	10			2					
Fatigue	3	2							
Depression		2		1					
Exercise tolerance			3	2					
Epididymitis					7				

CHF = congestive heart failure; Mild = noticeable, does not interfere with routine activities; Moderate = bothersome, requiring dose adjustment and/or supplemental therapy; Severe = may necessitate cessation of amiodarone; + = amiodarone-related; ± = ? amiodarone-related; − = doubt amiodarone-related.

certain that the drug had accumulated sufficiently to have a therapeutic effect, usually a minimum of 7 to 10 days. If a patient developed ventricular tachycardia or ventricular fibrillation again during this time the drug was simply continued at high dose for longer periods of time.

Both initial and maintenance doses of the drug are difficult to establish. The decision that loading has been sufficient and that the dose should be reduced is aided by several clues. Measurement of amiodarone serum levels is generally unobtainable in most hospitals. Measurement of reverse T_3 has been reported to be useful in determining when the drug has accumulated sufficiently (34). However, we most often used suppression of ambient ventricular arrhythmias and other electrocardiographic effects such as prolongation of the PR and QT intervals, widening of the QRS and development of sinus bradycardia and large U waves as indexes of drug effect. Documentation of corneal microdeposits is another clue that the drug has accumulated sufficiently, though keratopathy usually occurs after the antiarrhythmic effect has been achieved. Initially, the maintenance dose of amiodarone in our patients was a mean of 572 mg per day. More recently, the mean maintenance dose for patients who have taken the drug for at least 3 months has been 327 mg per day.

Our overall approach to the use of the drug has changed dramatically. With the first 70 patients the doses were reduced only if side effects were either moderate or severe. More recently, we have been routinely decreasing the dose before the appearance of side effects in an attempt to maintain a daily dose of 200 to 400 mg. Patients with supraventricular arrhythmias or less life-threatening arrhythmias may be controlled by giving even lower doses and thus further minimizing the possibility of side effects.

Antiarrhythmic efficacy. Amiodarone has been used in the United States primarily for patients with recurrent and refractory ventricular tachycardia and ventricular fibrillation. Amiodarone seems to be quite efficacious for suppression of ventricular arrhythmia, both simple and complex forms (1–12). Though convincing survival studies are still lacking, amiodarone seems to be useful in preventing ventricular tachycardia and may have a favorable effect on mortality in patients with the sudden cardiac death syndrome. Only 4 of 54 of our patients had ventricular fibrillation on follow-up, compared with 2 of 12 patients who had to stop amiodarone because of side effects. Though this comparison does not constitute a controlled study, at least the patients in both groups were selected for use of the drug by the same criteria, the one group having amiodarone discontinued simply because of noncardiac side effects and not because of antiarrhythmic inefficacy. Obviously, controlled randomized studies are needed to define the precise role of amiodarone in preventing recurrences of sudden cardiac death.

We did not recognize worsening of ventricular arrhyth- *mias with amiodarone in any of our patients as has been reported recently* (35–39). The four patients who died suddenly during follow-up had been on amiodarone for long periods of time. Amiodarone probably did not contribute to their subsequent fatal arrhythmias.

Electrophysiologic studies and Holter ambulatory monitoring. Our findings confirm the observations of others (22,23) that arrhythmias are invariably inducible during electrophysiologic testing on amiodarone therapy. Most of our electrophysiologic studies were performed many weeks after the patients had begun the drug, and usually the patients had corneal microdeposits at the time of programmed electrical stimulation. Thus, amiodarone does not seem to prevent the induction of ventricular arrhythmias by pacing techniques, although it is possible that certain characteristics of the arrhythmia induced might predict subsequent clinical success or failure of this agent (40,41). The finding that arrhythmias are inducible during amiodarone therapy is consistent with the concept that the myocardial substrate that could sustain an arrhythmia is still susceptible to catheter stimulation techniques at a time when the spontaneous arrhythmias are well controlled (42). This finding may mean that amiodarone in some way affects the trigger events or the initiating beats responsible for the induction of spontaneous ventricular arrhythmias.

Likewise, determination of a good response to amiodarone by Holter ambulatory electrocardiographic monitoring was difficult. Though counts of ventricular premature complexes decreased in patients who had a good response, and the counts increased in patients who subsequently had a recurrence of severe arrhythmias, the results were barely statistically significant. The findings overlapped enough between patients well controlled and those who would subsequently develop a recurrence of sustained ventricular tachycardia or ventricular fibrillation that we were uncertain when to alter therapy on the basis of results of Holter ambulatory electrocardiographic monitoring. In addition, the patients with the least arrhythmia on control monitor recordings seemed to have the worst outcome, making an assessment of drug efficacy on the basis of suppression of arrhythmia even more difficult.

Ventricular function. Many of our patients entered the study with severe congestive heart failure. During the period of follow-up, nine patients had worsening of the preexisting heart failure. However, overall ejection fraction in these patients has not systematically deteriorated with long-term amiodarone therapy. It is unknown whether the changes in clinical status in these nine patients were the result of amiodarone therapy or simply the progression of their underlying myocardial disease. Compared with some other new antiarrhythmic agents, amiodarone seems remarkably free of depressant effects on myocardial function.

The high mortality rate in our series of patients was most commonly caused by nonarrhythmic deaths. Death as a result of congestive heart failure was common. Other causes such as pulmonary embolism and recurrence of myocardial infarction further increased the mortality in this patient group. These findings simply emphasize the fact that many of these patients had terminal diseases. even though their arrhythmias could be well controlled.

Pulmonary toxicity. Pulmonary toxicity remains the most serious potential common side effect of this drug. Five patients in our series of the first 70 consecutive patients developed unequivocal changes consistent with pulmonary toxicity. One of these five patients died with pulmonary toxicity potentially contributing to his death. Another patient in the series of the next 60 patients also died with changes suggestive of pulmonary toxicity, and both patients had pathologic findings consistent with those reported before.

Predicting which patients will develop pulmonary toxicity has been difficult. Preexisting chronic lung disease with depression of diffusion capacity has weakly predicted which patients will develop pulmonary toxicity on long-term follow-up. Pulmonary toxicity can appear abruptly. either early or late during the therapy, and it commonly masquerades as viral or bacterial infection or worsening congestive heart failure. The relation to duration of therapy, maintenance dose and total dose remains unclear. The process appears to be a restrictive disease with thickening of pulmonary parenchyma and obliteration of alveolar spaces by proliferation of clear cells.

Effects of thyroid gland, cornea and liver. Thyroid function tests were commonly altered with an elevation of thyroxine (T_4). depression of triiodothyronine (T_3) and elevation of thyroid stimulating hormone. These findings are consistent with block by the drug of conversion of T_4 to T_3. However, only three patients were clinically hypothyroid requiring thyroid replacement.

All patients eventually developed corneal microdeposits except for the one patient who wore contact lenses. The microdeposits appeared as early as 5 weeks, and most patients had developed at least some corneal deposits by 2 to 3 months of therapy. Only rarely were these patients significantly bothered by ocular symptoms.

Changes in hepatic function paralleled those changes reported in other series, although they were statistically insignificant in our series. Many of our patients were extremely ill at the time the drug therapy was started. either with severe congestive heart failure or recurrent need for cardioversion or resuscitation. or both, so initial serum enzyme elevations were common in these patients. One patient may have developed worsening of his preexisting severe hepatic dysfunction.

Drug interactions. As previously reported. amiodarone interacts with a number of other medications used commonly by these patients (21). Elevation of digitalis, quinidine and procainamide levels have been documented when amiodarone was added to an otherwise stable regimen. In addition, amiodarone interacts with Coumadin, prolonging the prothrombin time. Initial 50% reduction of the dose of all of these agents is now routine for us.

Subjective side effects. Subjective side effects occurred in 93% of patients taking 600 mg per day, but only 19% of patients had to discontinue the drug because of these side effects. In all of these patients in whom the drug was ultimately stopped. it was first discontinued and then started at a lower dose in an attempt to continue the therapy.

Gastrointestinal side effects were most common but usually not severe. Neurologic side effects were more devastating. causing dose reduction or discontinuation in many patients, most of them early in the dosing schedule. Cutaneous and ocular side effects were also bothersome, but rarely limited the use of the drug.

Therapeutic implications. Amiodarone seems to be a useful drug for refractory arrhythmias. Its general utility will be limited by the long time period required before the drug has its full effect. the uncertainty of the proper dose in an individual patient and the potentially serious side effects of a drug that appears to accumulate in many tissues. The drug must be closely monitored in all patients. Using a maintenance dose of 600 mg per day, virtually all patients will have side effects. These side effects can be both bothersome and dangerous (43,44). with an incidence of pulmonary toxicity between 7 and 16%. Lower maintenance doses are necessary to minimize side effects, but it is unknown if the more severe side effects can be completely eliminated by dose reduction. The toxic to therapeutic ratio of amiodarone may be closer to unity than previously appreciated. Even though these patients are at risk of sudden death, the therapeutic strategy must be changed to eliminate side effects. Once the arrhythmia seems to be under good control as measured by elimination of ventricular premature complexes and spontaneous runs of ventricular tachycardia, the dose should be progressively decreased. The physician should monitor other factors such as the electrocardiogram, Holter monitor recordings. triiodothyronine (T_3) and corneal microdeposits to maintain an adequate amiodarone effect without allowing breakthrough arrhythmias that could initially present as sudden cardiac death.

Finally. randomized controlled studies are still needed to define the effect of amiodarone on survival. Our comparison of patients who continued the drug with those who had to discontinue the drug because of extracardiac side effects would suggest a beneficial effect of amiodarone on combined suppression of recurrent ventricular tachycardia and fibrillation. However, until better controlled survival studies are performed, amiodarone must still be considered simply an unproven experimental agent with great promise.

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