Efficacy of amiodarone during long-term treatment of malignant ventricular arrhythmias in patients with chronic chagasic myocarditis

Oral amiodarone was administered to 24 patients with chronic chagasic myocarditis (CCM) and malignant ventricular arrhythmias. Control 24-hour Holter recordings revealed frequent ventricular premature beats (VPBs) (157 to 2572/hr; mean 714 ± 125), multiform VPBs, and countless numbers of ventricular couplets in all patients, R-on-T phenomenon in 17 patients, and ventricular tachycardia in 21 patients. Amiodarone caused total and persistent suppression of ventricular couplets and tachycardia and greater than 93% reduction of VPB number in 22 patients, during a follow-up of 26.6 months (range 2 to 55 months). In 1 patient, ventricular couplets and tachycardia persisted despite the fact that a 98.2% reduction of VPB number was achieved. This latter patient was the only one in the whole group who experienced sudden death. The maximal antiarrhythmic effect was attained gradually after 3 to 26 weeks (mean 7.4). In four patients in whom treatment was discontinued after 3 to 12 months, the antiarrhythmic protection lasted 4 to 9 weeks. In nine patients the dose of amiodarone was 600 to 800 mg/day. In 15 patients the dose had to be increased to 800 to 1000 mg/day. Despite the presence of congestive heart failure in seven patients and intraventricular block in 17 patients, no limiting side effects were observed. Amiodarone proved to be extremely effective and safe against the most malignant ventricular arrhythmias of CCM. (Am Heart J 107:656, 1984.)

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Chronic chagasic myocarditis (CCM) is a frequent cause of sudden death in South America.[1,2] Multiple ECG abnormalities are common, including intraventricular and atrioventricular block, sinus node dysfunction, abnormal Q waves, and primary T wave changes.[1-4] The incidence of ventricular arrhythmias is inordinately high.[1,3-5] Severe cardiac failure and marked cardiomegaly are also common. Under such adverse circumstances, treatment of cardiac arrhythmias is difficult. Conventional antiarrhythmic drugs are scarcely effective and cardiac toxicity, favored by the underlying myocardial damage, may even result in the precipitation of sudden death. Thus the ventricular arrhythmias of CCM are one of the most demanding models on which a new antiarrhythmic agent can be tested.[5] In this report, we present our experience using amiodarone for the long-term treatment of malignant ventricular arrhythmias in patients with CCM, with particular emphasis on dose-response relationships, time interval required to reach the maximal antiarrhythmic effect, and persistence of the antiarrhythmic protection after drug withdrawal.

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METHODS

Patient population. The study population consisted of 24 patients. Clinical data are shown in Table I. The diagnosis of CCM was based on previously reported criteria.[1] Patients entered the study when one conventional ECG revealed ventricular premature beats (VPBs) showing two or more of the following features: multiform VPBs, R-on-T phenomenon, couplets, or runs of ventricular tachycardia (VT). Three or more consecutive VPBs were considered VT. Recurrent syncopal attacks occurred in eight patients, and two others experienced frequent dizzy spells. Eight patients complained of palpitations and seven had congestive heart failure. In 17 patients the following conduction disturbances were observed: right

Table I. Patient characteristics

Case	*Age*	*Clinical features*	*ECG findings*	*Cardiomegaly*
1	56	Asymptomatic	LVH; MN; PTW changes	+++
2	52	Syncopal attacks; 1 every 15-30 days	LV; PTW changes	++
3	62	Syncopal attacks; 1 every 3 years	RBBB + LAH	++
4	54	Palpitations	RBBB + LAH	++
5	34	CHF	LV; IRBBB + LAH; MN.	+++
6	62	CHF	Atrial fibrillation RBBB + LAH	++++
7	74	Dizzy spells CHF	LBBB	+++
8	36	Palpitations	RBBB	++
9	54	CHF	PTW changes	++
10	60	Dizzy spells	Sinus bradycardia RBBB + LAH; PTW changes	+++
11	53	Palpitations	Normal	+
12	37	Palpitations	LV; PTW changes	++
13	59	Syncopal attacks; 1 every month	RBBB + LAH	++
14	56	Palpitations	LVH	++
15	57	CHF; hypothyroidism	LV; IRBBB + LAH; MN; PTW changes	+++
16	49	Syncopal attacks; 1 every 7 to 30 days	RBBB + LAH; PTW changes	+++
17	40	Syncopal attacks; 1 every 6 months	Atrial fibrillation, RBBB + LAH	++
18	58	CHF	LAH; MN	++++
19	33	Palpitations	RBBB + LAH	++
20	44	Syncopal attacks; 1 every 2 months	RBBB + LAH; Sinus bradycardia; PTW changes	++
21	66	Syncopal attacks; 1 every 15 to 30 days	RBBB + LAH	—
22	62	Syncopal attacks; 1 every 4 to 5 days; CHF	LV; RBBB + LAH; first-degree AV block; MN; PTW changes	+++
23	37	Palpitations	RBBB + LAH	+++
24	40	Palpitations	PTW changes	+

Abbreviations and symbols:
CHF = congestive heart failure; I = incomplete; LAH = left anterior hemiblock; LBBB = left bundle branch block; LV = low voltages; LVH = left ventricular hypertrophy; MN = myocardial necrosis; PTW = primary T wave; RBBB = right bundle branch block; + = slight; ++ = moderate; +++ = severe; ++++ = extreme.

bundle branch block (RBBB) plus left anterior hemiblock (LAH) in 12 with first-degree atrioventricular (AV) block in one, incomplete RBBB plus LAH in two, RBBB in one, LAH in one, and LBBB in one. Severe to extreme cardiomegaly was documented in 10 patients. None of the 24 patients had been under antiarrhythmic or digitalis treatment prior to this study.

Study protocol. A control 24-hour ambulatory Holter recording was obtained with 445 Avionics equipment and two-channel recorders. Amiodarone was administered orally in a single or divided daily dose of 600 to 800 mg. Initially, 24-hour recordings were repeated at weekly intervals and evaluated to decide whether dose adjustments were necessary. If repetitive forms were not completely eliminated after 4 to 6 weeks, the dose was raised to 800 to 1000 mg/day. An insufficient reduction of VPB number (less than 90%) was not considered as an indication to increase the dose, because previous experience suggests that a greater efficacy can be achieved after longer periods of treatment. When the maximal antiarrhythmic effect was attained, Holter recordings were spaced out to every 15 to 90 days until 6 months of treatment, and every 3 to 6 months thereafter. The follow-up ranged from 2 to 55 months (mean 26.6 ± 4 months). In 14 patients showing intraventricular block, an ajmaline test[6] was performed before therapy to rule out a propensity to the occurrence of AV block.

Holter analysis of therapy. The Holter tapes were analyzed automatically by a computer (model 660 Avionics) to provide mean heart rate, number of VPBs/hr, as well as the curves of hourly variation for both VPBs and cardiac rate. The recordings were reanalyzed by two trained physicians and when discrepancies arose, a third observer analyzed the tapes. The number of extrasystolic configurations and ventricular couplets and tachycardia was established from real-time printout examination of events selected during visual control of the tapes. During the control study in seven patients all the runs of VT were printed out, counted, and their duration was measured in time and number of beats. In another 14 patients in whom

Table II. Ventricular arrhythmias on ambulatory monitoring in controls and during treatment

Case no.	*Number of beats in 24 hours*		*Number of VPBS in 24 hours*			*Number of extrasystolic foci*		*Couplets*		*VT (number of episodes)*	
	C	*A*	*C*	*A*	*% RED*	*C*	*A*	*C*	*A*	*C*	*A*
1	106,793	87,571	30,865	475	98.47	4	4	Yes	No	2350	—
2	93,487	83,117	8,456	14	99.84	5	2	Yes	No	2	—
3	86,878	76,385	5,330	73	98.64	5	4	Yes	No	—	—
4	129,261	91,689	9,381	594	93.67	4	4	Yes	No	68	—
5	101,402	81,805	7,187	165	97.66	5	4	Yes	No	2	—
6	130,436	81,152	51,151	1170	97.72	5	2	Yes	No	4000	—
7	97,842	76,518	9,980	8	99.92	4	2	Yes	No	11	—
8	91,670	60,950	26,150	12	99.95	5	1	Yes	No	3800	—
9	98,885	81,887	5,616	127	97.74	5	5	Yes	No	—	—
10	68,818	40,695	10,915	34	99.69	5	2	Yes	No	712	—
11	119,333	88,313	8,715	540	93.81	5	5	Yes	No	321	—
12	113,015	68,846	14,861	44	99.70	4	1	Yes	No	2	—
13	84,462	65,779	8,279	10	99.88	5	2	Yes	No	4	—
14	85,592	74,271	14,213	13,022	9.00	4	4	Yes	Yes	—	—
15	75,049	94,159	30,773	228	99.27	3	1	Yes	No	485	—
16	90,734	73,354	11,851	35	99.70	5	3	Yes	No	647	—
17	98,141	74,419	6,935	125	98.20	4	4	Yes	Yes	8	1
18	108,158	75,269	61,733	346	99.44	5	5	Yes	No	4018	—
19	114,156	78,398	8,677	26	99.71	5	1	Yes	No	520	—
20	95,040	70,401	27,360	158	99.42	5	2	Yes	No	315	—
21	133,727	103,710	5,220	355	93.20	5	6	Yes	No	150	—
22	82,497	80,028	3,780	2	99.95	5	2	Yes	No	3	—
23	103,150	88,223	29,624	106	99.64	5	5	Yes	No	1230	—
24	100,971	83,672	14,232	22	99.85	5	4	Yes	No	1694	—

Abbreviations: A = amiodarone; C = control; PSVBS = post supraventricular beats; PVPBS = post ventricular premature beats; RED = reduction; VT = ventricular tachycardia.

the salvos were exceedingly frequent, 1-minute strips were printed for each hour and an average was estimated. It was more difficult to quantitate the ventricular couplets, due to their extraordinary frequency. The shortest coupling interval of the VPBs and the occurrence of R-on-T was measured in strips lasting 1 minute during every hour of the recording. A similar analysis of the tapes obtained during amiodarone treatment was performed when the number of ectopic beats was greater than 300 in 24 hours. When VPBs were less than 300, all the ectopic beats were printed and counted.

Maximal antiarrhythmic effect. Testing an antiarrhythmic drug with a half-life as long as that of amiodarone poses particular problems. Although a large reduction of arrhythmias is apparent after 1 to 4 weeks, the full effect that the drug is able to provide does not occur until 3 to 5 months (3 to 5 half-lives) of continuous treatment. In the present context, we arbitrarily defined the *manifest* maximal antiarrhythmic effect (which usually occurs well before the full *potential* effect) as the one occurring whenever two or more successive Holter recordings showed a mean intervariation in VPB number of less than 2.5% in relation to the control study, and a similar presence or absence of ventricular couplets and tachycardia.

Persistence of drug effects. In four patients treatment was discontinued to assess the duration of the antiarrhythmic protection in Holter recordings obtained at weekly intervals. Treatment was restarted when ventricular couplets or tachycardia reappeared or when the VPB number approached the one observed in the control study.

Statistical evaluation. Student's *t* test for paired data (two-tailed) was used to assess the significance of changes in pairs of observations within patients. The results presented in this paper are a comparison of the baseline study against the Holter recording in which the greatest effect was documented. The latter was selected from a series of intratreatment recordings in which the maximal antiarrhythmic effect (as defined above) had been achieved.

RESULTS

Control studies (Table II). The VPB number ranged from 3,780 to 61,733 (mean 17,137 ± 3,055 VPBs) in 24 hours, and the total number of heart beats ranged from 68,818 to 133,727 (mean 100,395 ± 3,717 beats). The average hourly frequency of VPBs ranged from 157 to 2,572 (mean 714 ± 125 VPBs).

Shortest coupling interval (msec)				*R/T*			
C		*A*		*C*		*A*	
PVPBS	*PSVBS*	*PVPBS*	*PSVBS*	*PVPBS*	*PSVBS*	*PVPBS*	*PSVBS*
390	420	—	560	Yes	No	—	No
320	440	—	530	Yes	No	—	No
320	320	—	590	Yes	Yes	—	No
320	520	—	480	Yes	No	—	No
400	420	—	540	No	No	—	No
280	350	—	640	Yes	Yes	—	No
510	560	—	630	No	No	—	No
280	400	—	480	Yes	No	—	No
360	380	—	520	Yes	No	—	No
480	480	—	660	No	No	—	No
360	380	—	420	No	No	—	No
280	400	—	460	Yes	No	—	No
390	410	—	620	No	No	—	No
500	500	500	500	No	No	—	No
330	480	—	500	Yes	No	—	No
240	440	—	560	Yes	No	—	No
390	400	280	480	No	No	Yes	No
300	420	—	580	Yes	No	—	No
350	350	—	650	Yes	Yes	—	No
350	440	—	560	Yes	No	—	No
240	320	—	480	Yes	Yes	—	Yes
240	320	—	320	Yes	Yes	—	Yes
360	360	—	560	Yes	Yes	—	No
340	370	—	500	Yes	Yes	—	No

Seventeen patients showed five different VPB configurations, six showed four, and one showed three. All 24 patients had countless numbers of ventricular couplets and in all but one the couplets were present during each of the 24 hours of the Holter recording. Twenty-one patients had runs of VT and in 11 the VT salvos were present during each of the 24 hours. In most cases, the VT was multiform; uniform VT was only seen in five patients. R-on-T phenomenon was observed in 17 patients. In 14 patients the frequency of VPBs was persistently high all day long, whereas nine patients showed a substantial reduction during sleeping hours. There was a single case in whom the ventricular ectopy was more frequent during night sleep. In none of the 24 patients did the VPBs fail to occur for periods longer than 10 minutes. One of the eight patients with a history of syncopal attacks experienced a similar episode during the Holter recording, which showed VT reverting spontaneously after 36 seconds. Two other patients experienced dizziness, which coincided in one with a short run of VT lasting 7 seconds, and in the other with runs of ventricular flutter lasting 2 to 5 seconds.

Antiarrhythmic effects of amiodarone (Table II, Fig. 1). In 23 of 24 patients amiodarone caused a sustained reduction of the VPB number, which ranged from 93.2% to 99.9% (mean 94.8%; $p < 0.001$) (Fig. 1). The individual patient results are shown in Table II. Ventricular couplets were suppressed in 22 of 24 patients, and the runs of VT were eliminated in 20 of 21 patients. The shortest coupling interval was significantly prolonged from a mean of 411 msec to a mean of 534 msec ($p < 0.001$), and the R-on-T phenomenon was suppressed in 15 of 17 patients. The number of ectopic foci was not substantially affected.

In those patients in whom arrhythmias were less frequent during sleeping hours, a similar hourly pattern was preserved during the initial stages of treatment before achieving the maximal effect (Fig. 2). In the patients in whom the arrhythmias were persistently frequent throughout the 24 hours, the gradual reduction of the VPB number occurred in a parallel fashion. However, in five of the latter cases after a significant VPB reduction was achieved, VPBs were seen to occur only or predominantly during daily activities.

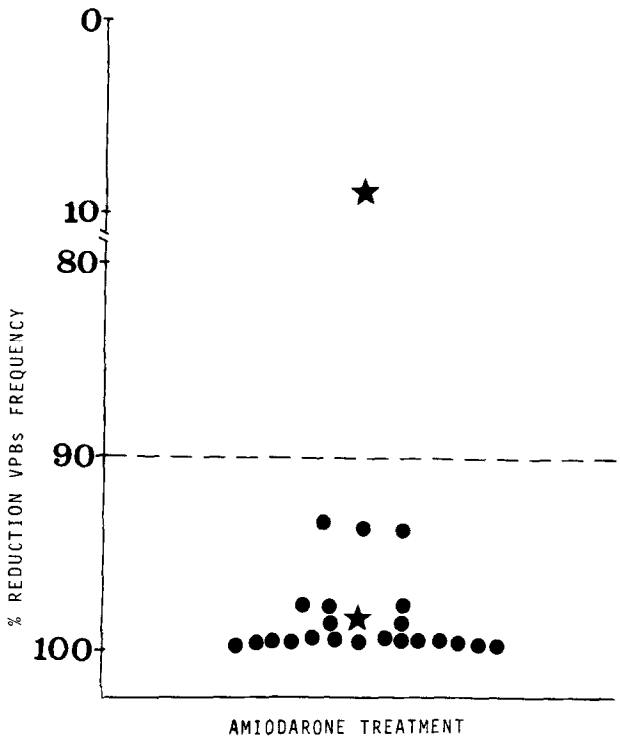

Fig. 1. Percentage reduction in frequency of VPBs with amiodarone in 24 patients with CCM. Twenty-two patients (91%) had a reduction of more than 93% in the number of VPBs with suppression of ventricular couplets and tachycardia. *Stars* represent the two cases in which ventricular couplets and VT were not suppressed.

Table III. Amiodarone dose; Latency of maximal antiarrhythmic effect and follow-up

Case no.	Dose (mg)		Maximal antiarrhythmic effects (wks)	Follow-up (mos)	Mortality
	Initial	Maximal			
1	600	600	4	24	
2	600	800	8	50	
3	600	600	4	42	
4	600	1000	12	48	
5	600	800	7	3	
6	800	1000	5	3	
7	600	600	4	38	+ Pulmonary edema
8	800	1000	26	48	
9	600	800	8	52	
10	600	800	8	15	
11	600	600	4	20	
12	600	800	5	48	
13	600	800	8	51	
14	600	800	—	3	
15	600	600	3	22	
16	800	1000	12	48	
17	600	1000	12*	5	+ Sudden death
18	800	1000	12	4	+ Suicide
19	600	600	4	55	
20	600	600	4	12	
21	800	800	4	24	
22	600	600	4	2	+ Pulmonary embolism
23	800	1000	4	3	
24	600	800	8	20	

*Persistence of couplets and ventricular tachycardia.

Cumulative action of amiodarone. The maximal antiarrhythmic effect was achieved gradually after 3 to 26 weeks (mean 7.4 ± 1 weeks). The individual patient periods of latency are shown in Table III, and a representative example is illustrated in Fig. 3. It should be noted that the reduction of VPB number reached a plateau after 4 weeks of treatment, whereas the heart rate was still falling during the 2 subsequent weeks. Unpublished observations from our laboratory indicate that the slowing of the heart rate, when studied through 24-hour Holter recordings, reaches a plateau only after 3 to 5 months of treatment.

Duration of antiarrhythmic protection. In four patients the administration of amiodarone was discontinued after 3,7,9, and 12 months of treatment, well after the ventricular arrhythmias had been successfully controlled. In the four cases ventricular couplets or tachycardia reappeared 28 to 45 days later. In two patients (cases No. 9 and 10), the number of VPBs returned to nearly control values after 4 and 5 weeks, respectively; in the other two patients (cases No. 2 and 12), the number of ectopic beats was still low (351 and 859 VPBs in 24 hours, respectively) when treatment was restarted after 4 and 6 weeks. Fig. 4 illustrates one of these four studies.

Dose-response relations. In nine patients the dose of amiodarone was 600 to 800 mg/day during the entire follow-up period. In 15 patients the dose had to be increased to 800 to 1000 mg/day. In four patients in whom the dose of 600 to 800 mg/day caused total or nearly total suppression of ventricular couplets and tachycardia and a greater than 90% reduction of the VPB number, the dose was reduced to 600 to 400 mg/day after 1 to 17 months of continuous treatment. In the four cases the latter dose failed to provide appropriate control of the arrhythmias. Fig. 5 illustrates one of these studies.

Follow-up and mortality (Table III). Four patients died during a follow-up period of 26.6 months (range 2 to 55 months). One died after 2 months, due to recurrent pulmonary embolism (case No. 23); another one (case No. 17) experienced sudden death after 5 months of treatment, 1 day after the last Holter recording which showed only 125 VPBs, but several

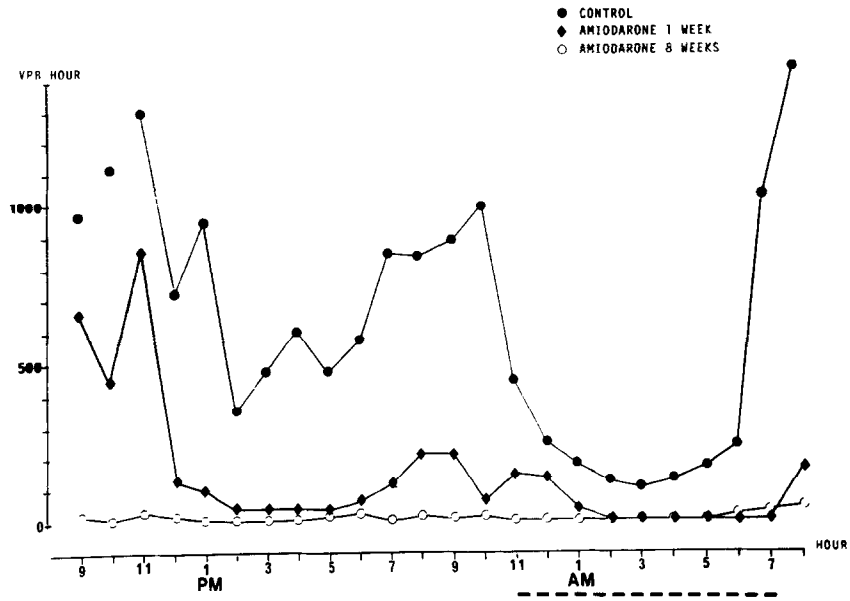

Fig. 2. Case No. 23. Progressively increasing effects of amiodarone on the hourly distribution of VPBs after 1 and 8 weeks of treatment. *Interrupted line* at bottom indicates sleeping hours.

couplets and one symptomatic episode of VT lasting 17 seconds. One patient died during acute pulmonary edema (case No. 7) after 38 months. The fourth patient committed suicide after 4 months of treatment (case No. 18). Syncopal attacks were suppressed in seven of eight patients, dizzy spells were eliminated in two out of two patients, and palpitations disappeared in six of eight patients. None of the seven patients with congestive heart failure showed adverse hemodynamic effects; on the contrary, a marked improvement was observed in three patients after control of the arrhythmias was achieved.

Side effects. All patients showed corneal microdeposits during slit-lamp examination of the eye, but none manifested impairment of visual acuity. Two patients had mild gastric discomfort. Two patients developed violaceous facial discoloration after 24 and 32 months of treatment. One patient developed clinical and laboratory evidence of thyrotoxicosis after 10 months of treatment, accompanied by reappearance of arrhythmias; he was successfully treated with antithyroid drugs without reducing the dose of amiodarone. Two patients showed marked sinus bradycardia (25 and 30 bpm) during sleep, and another had sporadic episodes of sinoatrial block which were also asymptomatic. In the first two cases, the dose of amiodarone was reduced from 800 and 600 to 600 and 400 mg/day. However, because of recrudescence of the arrhythmias, the dose was again increased to 1000 and 800 mg/day after 3 to 4

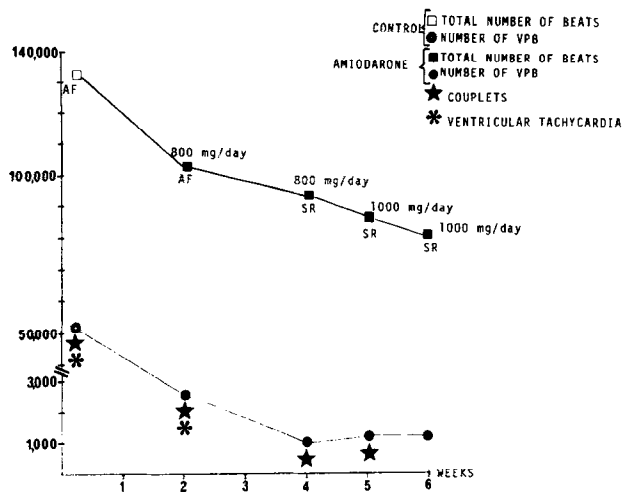

Fig. 3. Case No. 6. Progressively increasing effects of amiodarone on the heart rate *(upper curve)* and on the number of VPBs and presence of couplets and VT *(lower curve)* during the first 6 weeks of treatment. *AF* = atrial fibrillation; *SR* = sinus rhythm.

weeks, without further adverse effects. Two patients developed RBBB, 12 and 6 weeks after the initiation of treatment. This complication was probably related to latent fascicular damage in the right bundle branch.[7,8] One patient developed second-degree AV block after 3 years of treatment and a permanent pacemaker was implanted. Despite this variety of side effects, in none of the patients was treatment discontinued.

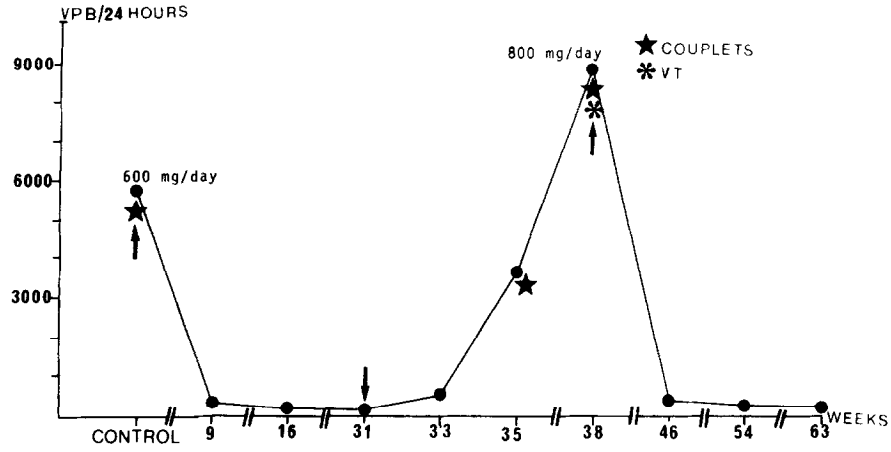

Fig. 4. Case No. 9. Effects of discontinuing the administration of amiodarone after 9 weeks of continuous treatment. *Left arrow,* Initiation of treatment (600 mg/day). *Middle arrow,* Interruption of treatment. *Right arrow,* Reinitiation of treatment (800 mg/day).

DISCUSSION

The chagasic model. Ventricular fibrillation (VF) is the most common cause of sudden death in patients with CCM.[1,2] When studied by serial Holter recordings,[5] these patients show extremely frequent, severe, and persistent ventricular arrhythmias. Thus in none of the 24 patients of the present study did ventricular arrhythmias fail to occur for periods longer than 10 minutes. Treatment of such ventricular arrhythmias is greatly complicated by the underlying myocardial damage, particularly the presence of heart failure and intraventricular block. Conventional antiarrhythmic agents may even increase the risk of VF, or aggravate a preexistent cardiac failure. Therefore the malignant ventricular arrhythmias of CCM constitute one of the most difficult tests to which a new antiarrhythmic drug can be subjected.[5]

Clinical efficacy of amiodarone. Amiodarone showed a remarkably high and sustained antiarrhythmic response in 22 of 24 patients (91%) with CCM during a follow-up period of 26.6 months. In each of the 22 responders the drug caused total suppression of ventricular couplets and tachycardia and a greater than 93% reduction of the VPB number. Similar results have previously been reported to occur in nonchagasic ventricular arrhythmias[9-11] when sufficiently high doses of the drug were administered during appropriately prolonged periods of time. There were two nonresponders. In one, amiodarone was truly ineffective; in the other, ventricular couplets and tachycardia persisted despite the fact that a 98.2% reduction of VPB number had been achieved. This latter patient was the only one in the whole group who experienced sudden death. This potent antiarrhythmic action was paralleled by a clear symptomatic improvement, which was particularly important in those patients with a history of syncopal attacks. Although appropriate statistics on the incidence of sudden death in CCM are not available, our study suggests that amiodarone might have played a role in preventing the occurrence of sudden death in many of our patients. This view is strongly supported by recent studies,[10,11] indicating that amiodarone caused a decrease in the propensity for recurrencies of VT and VF in patients with nonchagasic malignant arrhythmias. In this regard, a definite advantage of amiodarone would be its prolonged duration of action, demonstrated in four cases of the present study. Essentially similar results were reported by Nademanee et al.[12] in nine patients with nonchagasic ventricular arrhythmias in whom drug withdrawal was carried out in order to document efficacy of the drug. In only one of the nine patients did the arrhythmia fail to reappear.

Dose-response relations. The doses required to achieve a maximal antiarrhythmic effect ranged from 600 to 1000 mg/day. These are rather high doses. Furthermore, the maximal antiarrhythmic response was only obtained after a latency of 7.4 weeks. This is also an extremely long interval. However, the dose-response relationships of amiodarone, as well as the duration of both the latency and the antiarrhythmic protection, may vary substantially in different arrhythmias. For example, repetitive supraventricular tachycardias are commonly controlled with doses as low as 150 to 200

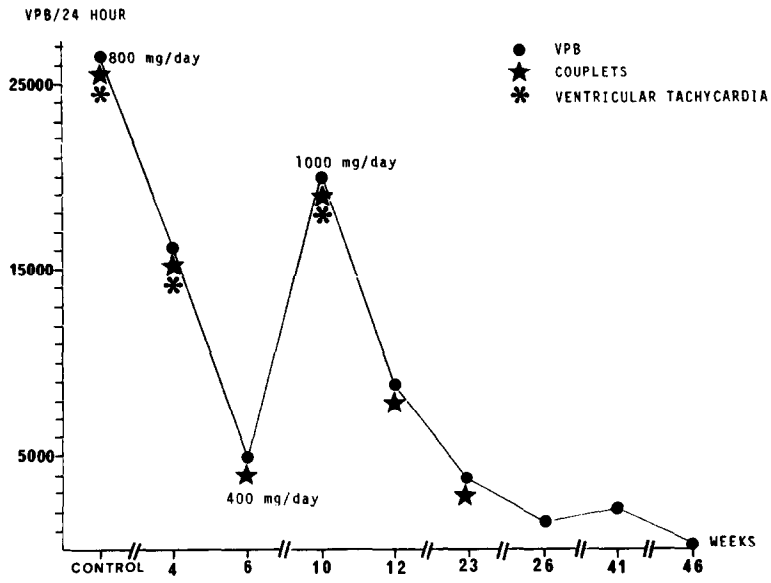

Fig. 5. Case No. 8. Effects of different doses of amiodarone on the frequency of VPBs and the presence of ventricular couplets and VT.

mg/day, after a short (10 days) loading period with 600 mg/day.[13] In those cases prevention of the tachycardias can be achieved in 5 to 10 days, and duration of the antiarrhythmic protection (when withdrawing the drug after several months of treatment) may last 30 to 60 days, and sometimes up to 150 days.[14,15] Patients with recurrent atrial fibrillation require relatively higher doses, around 400 mg/day after a loading period of 15 to 30 days with 600 to 900 mg/day, while the latency is somewhat longer and the duration of the effects is somewhat shorter. On the other hand, the prevention of sustained recurrent symptomatic VT requires a maintenance dose of around 750 mg/day, after loading doses of 600 to 2000 mg/day.[16] More recently, we have reported[17] that ventricular arrhythmias of patients with chronic stable ischemic heart disease can be controlled with a maintenance dose of 590 mg/day. Within this diversity of circumstances the arrhythmias of CCM may be placed close to the upper end of the spectrum.

Therapeutic threshold. These observations support the view that each type of arrhythmia and probably each arrhythmic patient has its/his own therapeutic threshold. Thus during the progressively increasing effects of amiodarone documented in our study, runs of VT disappeared first, whereas suppression of couplets required a longer period of treatment, and an even longer time was necessary to attain a maximal reduction of the VPB number (Figs. 4 and 5). Therefore there seems to be a first therapeutic threshold for VT, a second and higher threshold for couplets, and a third and even higher threshold for maximal reduction or suppression of VPBs. However, exceptions may occur, as exemplified by a single patient in our study in whom despite a nearly total suppression of isolated VPBs, ventricular couplets and VT (and a high risk of VF) still persisted. It is remarkable that multiform VPBs were not or were scarcely modified by amiodarone, despite the marked effects on ventricular couplets and VT and the number of VPBs. These results suggest that, whenever multiform VPBs are as frequent as observed in CCM, their therapeutic threshold is probably the highest.

Side effects. It is important that amiodarone provided its antiarrhythmic response at a relatively small iatrogenic cost, particularly in view of the high doses employed, the long duration of treatment, the presence of congestive heart failure in seven patients, and the occurrence of intraventricular block in 17 of the 24 patients. Several side effects were observed in the present study, but altogether, they were of a mild character and did not imply the need to interrupt treatment. In one of the patients a permanent pacemaker had to be implanted because of the occurrence of second-degree AV block. However, it is not unlikely that this complication, probably the worst in our study, was unrelated to drug therapy and was really due to the natural course of the disease. Some more important but rare complications have been reported elsewhere,[18-20] but in the present study amiodarone was virtually devoid of *limiting* adverse effects.

Mechanisms of action. The mechanisms underlying the extraordinary antiarrhythmic potency of amiodarone are still unclear. Prolongation of the action potential duration may play a role,[21] but the magnitude of this effect[22] does not seem enough to explain the drug efficacy. Recent studies from our laboratory[22] show that amiodarone causes a significant prolongation of the absolute refractory period at the expense of the relative refractory period, so that premature responses fail to be conducted, or are conducted at a rapid rate of depolarization.

The half-life of amiodarone has been estimated in around 30 days.[23, 24] This is related to its cumulative action, which explains both the gradual commencement of the antiarrhythmic effects and the persistence of the pharmacologic protection. In our patients, the maximal antiarrhythmic effects were attained progressively after 2 to 26 weeks; in four patients in whom treatment was interrupted after several months, the antiarrhythmic protection was shown to last 4 to 9 weeks. It is tempting to speculate that because of its slow cumulative effect, amiodarone is likely to impregnate each cardiac cell more homogeneously than short-acting drugs that must be administered every several hours to keep a rather unstable plasma (and tissue) level. This is probably the main reason why classical antiarrhythmic drugs may eventually cause VF. Clinical evidence indicates that the likelihood of an arrhythmogenic effect of amiodarone is much less than that of other antiarrhythmic agents, and that the cumulative effect may be one of the main causes of the antiarrhythmic efficacy of the drug.

Conclusions. Epidemiologic surveys in Argentina have shown that about 2,500,000 people have chronic Chagas infection, and that 500,000 suffer from CCM.[25] Similar figures have been reported from other Latin American countries.[26-31] Many of those patients are at high risk of sudden death. The availability of antiarrhythmic drugs capable of preventing this complication is therefore of the utmost importance. Our results suggest that amiodarone is extremely effective against the most malignant ventricular arrhythmias of CCM, and may eventually prevent the occurrence of sudden death in many of those patients.

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Abnormal quinidine binding in survivors of prehospital cardiac arrest

Quinidine binding was studied in 15 survivors of prehospital cardiac arrest and was compared to 18 normal individuals and 20 patients with coronary artery disease. The unbound quinidine fraction was 6.3 ± 2.8% in the survivors of prehospital cardiac arrest, a value significantly lower than normal individuals (unbound quinidine fraction = 9.9 ± 3.0%, $p < 0.005$). Furthermore, unbound quinidine fraction correlated with interdose quinidine half-life in the six survivors of prehospital cardiac arrest where this could be measured ($r = 0.79$, $p < 0.05$). The resultant quinidine interdose half-life was significantly prolonged (10 ± 3 hours) when compared to normal (6 ± 2 hours, $p < 0.02$). The reduction in free drug fraction in cardiac arrest survivors was a nonspecific finding in that free drug fraction was also reduced in the patients with coronary artery disease (unbound quinidine fraction = 7.4 ± 3%) and was independent of the α-1-glycoprotein concentration. Therefore survivors of prehospital cardiac arrest have a mean 40% reduction in free quinidine drug fraction which results in less free drug at any given total drug concentration and may relate to quinidine pharmacokinetics and pharmacodynamics in this patient group. (Am Heart J 107:665, 1984.)

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Quinidine is a widely used antiarrhythmic agent which is highly bound to plasma proteins.[1] Abnormalities in the binding of quinidine, either increased or decreased binding, have been noted in a variety of acute and chronic disease settings.[2-5] Since quinidine binding varies significantly even in normal individuals,[1] abnormalities in binding in various disease states further erodes the tenuous relationship between total and free (active) drug concentrations.