

Improved survival with amiodarone in patients with hypertrophic cardiomyopathy and ventricular tachycardia

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SUMMARY The effect of amiodarone on survival was assessed in patients with hypertrophic cardiomyopathy and ventricular tachycardia in a drug trial with historical controls. During 1976 and 1977, 24 hour (seven) or 48 hour (79) electrocardiographic monitoring was performed in 86 consecutive patients; 24 had ventricular tachycardia and received conventional antiarrhythmic agents. Nineteen clinical, echocardiographic, and haemodynamic features were assessed. Seven patients died suddenly during follow up of three years; of these, five had continued to have ventricular tachycardia and two had no documented ventricular tachycardia. During 1978 and 1979, ventricular tachycardia was detected during 48 hour electrocardiographic monitoring in 21 of the next 82 consecutive patients with hypertrophic cardiomyopathy. They received amiodarone (150-400 mg/day, median 300); ventricular tachycardia was suppressed in all during repeat 48 hour electrocardiographic examination. Two patients died suddenly during a three year follow up, but neither belonged to the amiodarone treated group with ventricular tachycardia. The clinical and haemodynamic variables were similar in patients taking amiodarone and conventional agents. The fact that control of ventricular arrhythmia with amiodarone is significantly associated with improved survival suggests that amiodarone may prevent sudden death in patients with hypertrophic cardiomyopathy and ventricular tachycardia.

The high risk of sudden death was one of the earliest recognised features and is the most important problem in the management of patients with hypertrophic cardiomyopathy.¹⁻⁶ Approximately 25% of patients show bursts of ventricular tachycardia during electrocardiographic monitoring, and they are at even greater risk.⁷⁻¹¹ Amiodarone has been available in the United Kingdom since 1973, initially for use on compassionate grounds in specified patients with refractory arrhythmia. Once its efficacy was demonstrated^{12,13} we have since 1978 extended its use to patients with hypertrophic cardiomyopathy and ventricular arrhythmia.¹⁴ We now report our experience of the effect of amiodarone on survival of patients with hypertrophic cardiomyopathy and ventricular

tachycardia. We compared the three year survival of 24 consecutive patients with ventricular tachycardia who had been treated initially with conventional antiarrhythmic agents and of the next 21 consecutive patients with ventricular tachycardia, who received amiodarone.

Patients

One hundred and sixty eight consecutive patients with hypertrophic cardiomyopathy aged ≥ 5 years who were seen at this hospital during 1976 to 1979 underwent ambulatory electrocardiographic monitoring with no cardioactive treatment other than beta adrenergic blockers, verapamil, or digoxin. Hypertrophic cardiomyopathy is defined as a heart muscle disorder of unknown origin that is characterised by unexplained hypertrophy of a non-dilated left ventricle.¹⁵ The diagnosis was confirmed in 158 patients by the demonstration of unexplained left ventricular hypertrophy during cross sectional echocardiography. The pattern of hypertrophy was classified as asym-

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metrical, symmetrical, or predominantly distal ventricular.¹⁵ In the remaining patients echocardiography was technically difficult and the diagnosis relied on clinical, haemodynamic, and angiographic features.⁴ No patient had documented systemic hypertension. Cardiac catheterisation had been performed in 142 patients, in 112 of them within three years of the study. Patients were considered to have a left ventricular gradient if the difference under basal conditions or after provocation was ≥ 30 mm Hg.

Methods

During 1976 and 1977 ventricular tachycardia, defined as ≥ 3 consecutive ventricular extrasystoles with a mean rate of > 120 beats/minute, was detected in two of seven patients who underwent 24 hour electrocardiographic monitoring and in 22 of 79 who underwent 48 hour electrocardiographic monitoring. Details of these 86 patients have been published.¹⁰ Symptomatic treatment in the 24 with ventricular tachycardia included propranolol in 15 (63%), diuretics in four (17%), and verapamil in one (4%). They received disopyramide 400–800 mg daily, mexiletine 600 mg daily, or quinidine 500 mg daily; eight received two of these drugs and one was given all three. Treatment was guided by electrocardiographic monitoring and the presence or absence of side effects; plasma drug concentrations were not measured. Ventricular tachycardia was suppressed in five of the 24.

During 1978 and 1979, 21 of the next 82 patients had ventricular tachycardia during 48 hour electrocardiographic monitoring. Symptomatic treatment in these 21 included propranolol in 16 (76%), diuretics in seven (33%), and verapamil in two (10%). They received amiodarone 400–1200 (mean 800) mg daily for one week followed by 200 or 400 mg daily for the

initial maintenance period (four weeks). The dose was then adjusted 1–7 (median 2) times during the three years in an attempt to achieve the minimum effective maintenance dose. Details of their management, particularly of the relation of dose, plasma drug concentration, efficacy, and side effects, have been published.¹⁶ In brief, plasma amiodarone concentrations were appropriate for the daily dose, and none of these 21 patients experienced serious side effects. Ventricular tachycardia was suppressed with 150–400 (median 300) mg daily.

The consecutive patient populations with ventricular tachycardia were compared using 19 clinical, echocardiographic, and haemodynamic variables; their survival was assessed during an outpatient visit and was compared 36 months after the detection of ventricular tachycardia using Fisher's exact test and life table analysis.¹⁷ Death was defined as sudden if it was unexpected and instantaneous. No patient was lost to follow up.

Results

The mean and maximum rate and duration of ventricular tachycardia were similar in the two treatment groups; the incidence of associated ventricular and supraventricular arrhythmias was marginally higher in the amiodarone group (Table 1). There were no significant differences in clinical, prognostic, echocardiographic, or haemodynamic features between the two groups (Tables 2 and 3).

Of patients with ventricular tachycardia, five of 24 who were treated with conventional antiarrhythmic drugs died suddenly and unexpectedly within three years, whereas all 21 who received amiodarone survived three years or longer (Fig. 1). Treatment with amiodarone was associated with improved survival ($p < 0.04$). The overall mortality in patients who did not have ventricular tachycardia was similar during

Table 1 *Arrhythmias in two consecutive groups of patients with ventricular tachycardia treated with conventional antiarrhythmic agents or amiodarone. Figures are numbers (percentages)*

	Conventional agents (n=24)	Amiodarone (n=21)
Atrial fibrillation	3 (13)	3 (14)
Supraventricular tachycardia or paroxysmal atrial fibrillation	9 (43)	13 (68)
> 200 ventricular extrasystoles/day	12 (50)	11 (52)
Multiform and paired ventricular extrasystoles	19 (79)	19 (90)
Rate of ventricular tachycardia/min:		
Maximum	210	190
Mean	142	146
Beats of ventricular tachycardia:		
Maximum	27	22
Mean	8	7

Table 2 *Clinical and prognostic features in patients with ventricular tachycardia treated with conventional agents or amiodarone. Figures are numbers (percentages) of patients unless stated otherwise*

	Conventional agents (n=24)	Amiodarone (n=21)
Mean (SD) age (yr)	46 (12)	44 (13)
Mean (SD) follow up (yr)	6 (5)	7 (7)
Mean (SD) duration of symptoms (yr)	9 (8)	8 (7)
Male	16 (67)	14 (67)
Female	8 (33)	7 (33)
Family history of hypertrophic cardiomyopathy and sudden death	5 (21)	3 (14)
Syncope	5 (21)	8 (38)
Severe dyspnoea	5 (21)	6 (29)
Chest pain	10 (43)	10 (48)

Table 3 *Echocardiographic and haemodynamic features in patients with ventricular tachycardia treated with conventional agents or amiodarone. Figures are numbers (percentages) of patients unless stated otherwise*

	1976-77 (n=24)	1978-79 (n=21)
Asymmetrical septal hypertrophy	10 (43)	8 (38)
Symmetrical left ventricular hypertrophy	10 (43)	11 (52)
Mean (SD) thickness of thickest segment (mm)	22 (6)	21 (4)
Left ventricular gradient \geq 30 mm Hg	11 (50)	10 (50)
Mean (SD) left ventricular end diastolic pressure (mm Hg)	19 (6)	17 (7)

the earlier and later treatment periods (two of 62 and three of 61 respectively).

Discussion

Approximately one third of patients with hypertrophic cardiomyopathy die suddenly within 10 years of diagnosis.^{5,6} Children and those with a family history of hypertrophic cardiomyopathy and sudden death, previous syncope episodes, or ventricular tachycardia during electrocardiographic monitoring are at particular risk.^{2-6,10,11} In this study of adults with hypertrophic cardiomyopathy and ventricular tachycardia there was a 21% three year mortality from sudden death in the 24 patients who were treated with conventional antiarrhythmic drugs compared with no deaths among the next 21 consecutive patients who took amiodarone, all of whom survived at least three years (Figure 2). Though conventional antiarrhythmic agents may in theory increase the incidence of sudden death,¹⁸ we did not observe putative mechanisms for this, for example, QT prolongation or multiform ventricular tachycardia. Overall, therefore, we interpret these results as suggesting that amiodarone may prevent sudden death in these high risk patients.

For historical reasons this comparison of survival during treatment with conventional antiarrhythmic drugs and amiodarone could not be randomised but was based on two consecutive patient populations with hypertrophic cardiomyopathy who had ventricular tachycardia detected during electrocardiographic monitoring. Soon after our recognition of the high incidence of ventricular arrhythmia we entered seven of the patients with ventricular tachycardia (included in the conventional treatment group) into a comparative study of the antiarrhythmic effect of disopyramide and mexiletine. Arrhythmias were not controlled, side effects were common, and four of the seven died suddenly during treatment. Amiodarone had just received a restricted licence in the United Kingdom; it was quickly shown to be an effective

antiarrhythmic agent in these patients,¹⁴ and a randomised prospective study in patients with hypertrophic cardiomyopathy and ventricular tachycardia was never feasible. To date no patient has died suddenly while taking amiodarone either in this comparative series of patients with ventricular tachycardia or in our larger series of patients with hypertrophic cardiomyopathy and other arrhythmias.¹⁶ It would not now be possible for us to justify a randomised prospective study of amiodarone and conventional antiarrhythmic agents in patients with hypertrophic cardiomyopathy and ventricular tachycardia.¹⁹

The characteristics of these two consecutive patient populations with hypertrophic cardiomyopathy and ventricular tachycardia were comparable. Clinical and prognostic features, the extent and distribution of left ventricular hypertrophy, left heart filling pressures, and the proportion of patients with left ventricular gradients were similar in the two groups. The characteristics of the episodes of ventricular tachycardia were also similar in patients who received conventional antiarrhythmic drugs and those who received amiodarone, while the incidence of associated supraventricular and ventricular arrhythmias was not

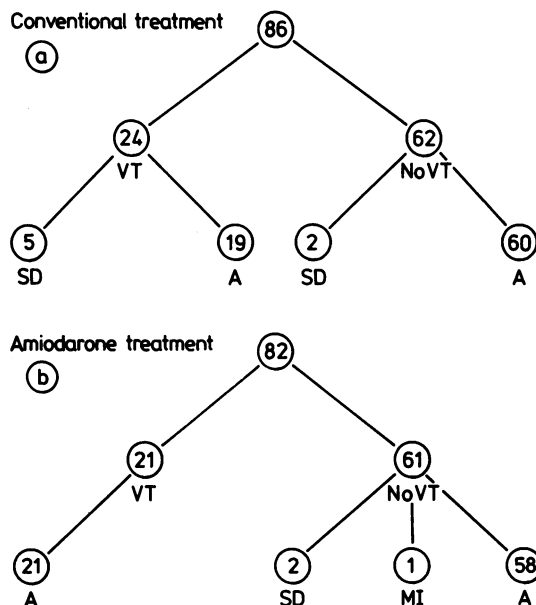


Fig. 1 *Clinical outcome (a) in 86 consecutive patients undergoing electrocardiographic monitoring during 1976 and 1977, of whom 24 with ventricular tachycardia (VT) were treated with conventional antiarrhythmic drugs; and (b) in 82 consecutive patients undergoing electrocardiographic monitoring during 1978 and 1979, of whom 21 with ventricular tachycardia (VT) were treated with amiodarone. SD, sudden death; A, alive; MI, died of documented myocardial infarction.*

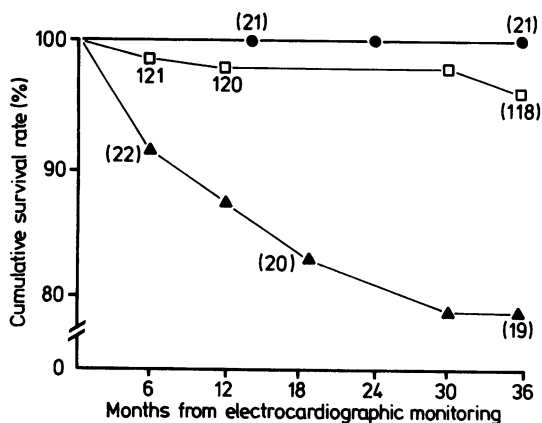


Fig. 2 Cumulative survival rate for 24 patients with ventricular tachycardia treated with conventional antiarrhythmic agents (▲), 21 with ventricular tachycardia treated with amiodarone (●), and 123 without ventricular tachycardia (□). The probability of cardiac death is equal to the total number of deaths for the year divided by the adjusted number at risk minus the number of deaths due to other causes.¹⁷

significantly greater in the latter group. In the only other large series, from the National Institutes of Health, four of 17 patients with ventricular tachycardia, who received conventional antiarrhythmic agents, died suddenly or experienced cardiac arrest during three years¹¹; thus the annual mortality from sudden death of 8.6% was similar to our own finding in these patients with ventricular tachycardia. The annual mortality from sudden death in medically treated patients without ventricular tachycardia was also similar in the National Institutes of Health series (two of 66) and in our two consecutive populations (two of 62; and two of 61). During the period of the study we used the same approach to the treatment of symptoms, and we corroborated the fact that our referral sources, diagnostic criteria, and indications for electrocardiographic monitoring did not alter.

Of the many potential causes of sudden death in hypertrophic cardiomyopathy, primary ventricular arrhythmia and acute reduction in left ventricular volume from decreased afterload or filling pressure are the most likely to be important. Amiodarone does not alter systolic or diastolic blood pressure or radionuclide indices of left ventricular function,²⁰ so it is logical to assume that amiodarone prevents sudden death through suppression of episodes of ventricular arrhythmia. It is also possible that an unfavourable haemodynamic alteration is the initiating event and that the clinical outcome is determined by the electrical behaviour of the myocardium. If this hypothesis is correct amiodarone may be effective not so much by suppressing non-sustained episodes of

ventricular tachycardia as by promoting electrical stability of the myocardium²¹ and may warrant evaluation in other high risk patients with hypertrophic cardiomyopathy.

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