Arrhythmia in hypertrophic cardiomyopathy

II: Comparison of amiodarone and verapamil in treatment

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SUMMARY The antiarrhythmic effects of amiodarone and verapamil were compared in 19 patients with hypertrophic cardiomyopathy complicated by refractory arrhythmias. While verapamil did not reduce the incidence of arrhythmia, amiodarone abolished ventricular tachycardia in 10 of 13 patients and significantly reduced the number of ventricular extrasystoles. In addition, sinus rhythm was restored by amiodarone in three of five patients with longstanding atrial fibrillation.

Death is a common complication of hypertrophic cardiomyopathy and is usually sudden and unexpected.¹⁻³ Serious ventricular arrhythmia is also common,⁴ and is associated with sudden death.⁵ During the past decade beta-adrenergic blockers have been the mainstay of treatment. While they appear to relieve symptoms they do not reduce the incidence of arrhythmia.⁶ Verapamil, which has been advocated, may improve symptoms and exercise tolerance⁷ and possibly influence myocardial hypertrophy^{8, 9} but there is little knowledge of the antiarrhythmic effect of this drug in this disease. Amiodarone is effective in a wide variety of ventricular¹⁰ and supraventricular arrhythmias.¹¹ We therefore decided to compare amiodarone and verapamil in the treatment of arrhythmia in hypertrophic cardiomyopathy.

Methods

Routine 24-hour ambulatory electrocardiographic monitoring is performed at least once a year in patients with hypertrophic cardiomyopathy followed up at the Hammersmith Hospital. Patients were selected for this study if electrocardiographic monitoring disclosed: (1) paroxysmal atrial fibrillation or supraventricular tachycardia; (2) atrial fibrillation with a rapid ventricular response (greater than 100 a minute) despite treatment with digoxin and beta-adrenergic blockers; (3) frequent or complex ventricular extrasystoles or ventricular tachycardia.

All drugs except diuretics were stopped for one week and the following performed as a baseline. (1)

physical examination including measurement of the blood pressure at rest in the supine position; (2) electrocardiogram and chest x-ray; (3) thyroid and liver function tests; (4) graded maximal treadmill exercise using a modified Bruce protocol¹²; (5) 72-hour ambulatory electrocardiographic monitoring which was analysed by a technician using a Reynolds Pathfinder system.

For convenience, a modification of the grading system of Ryan *et al.*¹³ for ventricular arrhythmia was used: grade 1, no more than 30 ventricular extrasystoles in any hour of monitoring; grade 2, more than 30 ventricular extrasystoles in any hour of monitoring; 3a, multiform ventricular extrasystoles; 3b, pairs (two consecutive ventricular extrasystoles); grade 4, multiform and paired ventricular extrasystoles; grade 5, ventricular tachycardia (three or more complexes in succession). The investigations were repeated after each of three treatment periods. The first consisted of verapamil 240 mg daily for one week and 480 mg daily for three weeks; the second, amiodarone in a loading dose of 1200 mg daily for one week; and the third, amiodarone in a maintenance dose of 400 mg daily for one month. Ophthalmological examination was performed after each of the amiodarone treatment periods.

Patients

Nineteen patients with hypertrophic cardiomyopathy and arrhythmia were studied. Thirteen of the patients had ventricular tachycardia. They had previously failed to respond to mexiletine or disopyramide, either alone or in combination with propranolol. Five patients had atrial fibrillation with a poorly controlled ventricular rate despite beta-adrenergic blockers and

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digoxin, and one patient had paroxysmal atrial fibrillation.

In all patients the diagnosis of hypertrophic cardiomyopathy was made on the typical clinical features,¹⁴ M-mode echocardiography,¹⁵ and left ventricular angiography.¹⁶ Patients were considered to have a significant left ventricular outflow tract gradient if the difference measured under basal conditions or with provocation (amyl nitrate inhalation or Valsalva manoeuvre) was equal to or exceeded 20 mmHg. Thirteen had a significant gradient (nine at rest and four on provocation) and six did not. The mean left ventricular end-diastolic pressure was 17 mmHg (range 5 to 35).

Eleven of the patients were men and eight were women; they ranged in age from 32 to 72 years, mean 50. The diagnosis of hypertrophic cardiomyopathy was established one to 16 years, mean seven, before the study. Seven patients had chest pain on exertion, three had syncope, 14 had dyspnoea (New York Heart Association class 2), and one had dyspnoea class 3. Two patients were asymptomatic.

Statistical analysis

Where appropriate the McNemar test, a modification of the χ^2 test, was used to assess statistical significance. The two sample t test was used to test the difference between two means and the two sample Wilcoxon test was used to differentiate between the two samples when the data were not normally distributed.

Results

Amiodarone was well tolerated by all the patients, but three developed cardiac failure during treatment with verapamil. The side effects are summarised in Table 1. During the loading period with amiodarone six patients exhibited excessive prolongation of the thrombotest, which was restored to the therapeutic range when the daily dose of warfarin was halved. One-third of the patients had sleep disturbance: nightmares, excessive dreaming, or early morning wakening. Fourteen patients had mild photosensitivity during maintenance amiodarone treatment. No patient had symptoms of thyroid disturbance.

Supraventricular arrhythmias were detected during electrocardiographic monitoring in all patients (Table 2). Nine had episodes of supraventricular tachycardia, of whom five had frequent atrial extrasystoles (>30 an hour). Verapamil produced no significant change in the number of patients with these arrhythmias and the mean daily number of atrial extrasystoles (295) was unchanged (320). On amiodarone none had supraventricular tachycardia, only one had frequent atrial extrasystoles, and the mean daily number of atrial extrasystoles was significantly reduced during loading (86, $p<0.03$) and maintenance treatment (20, $p<0.001$). Five patients were in atrial fibrillation, all for at least five years: in three sinus rhythm was restored during the loading period and in two it was maintained at six months (Fig.).

Table 1 Side effects during treatment with amiodarone and verapamil

	Amiodarone loading (n=19)	Amiodarone maintenance (n=19)	Verapamil (n=19)
Photosensitivity	3	14	0
Sleep disturbance	8	6	0
Headache	2	0	2
Nausea	4	0	1
Tremor	3	3	0
Thyroid	0	0	0
Corneal deposits	4 (of 6): mild	5 (of 5): mild	0
Anticoagulant potentiation	6 (of 7)	0	0
Cardiac failure	0	0	3

Table 2 Supraventricular arrhythmia detected during 72-hour ambulatory electrocardiographic monitoring off medication, on verapamil, and on amiodarone

	Off medication		Verapamil		Amiodarone loading dose		Amiodarone maintenance dose	
	(n=13) No.*	%	(n=10) No.*	%	(n=10) No.*	%	(n=13) No.*	%
Atrial extrasystoles								
None	0	0	0	0	4	40	4	31
≤30/hour	8	61	5	50	5	50	8	62
>30/hour	5	38	5	50	1	10	1	8
Supraventricular tachycardia								
1-3 episodes/day	6	46	4	40	0	0	0	0
>3 episodes/day	3	23	2	20	0	0 †	0	0 †

*Patients in atrial fibrillation excluded.

† $p<0.01$.

Fig. Restoration of sinus rhythm after amiodarone. Electrocardiographic recording (leads I, II, and III). Baseline: established atrial fibrillation which failed to convert to sinus rhythm after DC cardioversion (250 joules). Amiodarone: recording showing restoration of sinus rhythm after five days on amiodarone 1200 mg daily.

Experience with the ventricular arrhythmias detected during ambulatory electrocardiographic monitoring is presented in Table 3. Nine patients had frequent ventricular extrasystoles (>30 an hour) and 10 had ventricular tachycardia while not being treated. Amiodarone (both loading and maintenance doses) significantly reduced the number of patients who had frequent ventricular extrasystoles and the number with ventricular tachycardia whereas verapamil did not.

The majority of patients with ventricular tachycardia did not have severe symptoms (Table 4): 11 experienced dyspnoea exclusively during moderate exercise, only three had syncopal episodes, and one patient was asymptomatic. Their mean left ventricular end-diastolic pressure was 17 mmHg, identical to that found in our series of 254 patients with hypertrophic cardiomyopathy.³ The mean number of episodes of ventricular tachycardia off medication (5.2) and during verapamil (6.1) was similar but was

Table 3 Ventricular arrhythmia detected during 72-hour ambulatory electrocardiographic monitoring off medication, on verapamil, and on amiodarone

Arrhythmia grade	Off medication		Verapamil		Amiodarone loading dose		Amiodarone maintenance dose	
	(n=19)		(n=16)		(n=15)		(n=19)	
	No.	%	No.	%	No.	%	No.	%
1 (≤30 VES/h)	10	53	10	63	14	93	16	84
2 (>30 VES/h)	9	47	6	38	1*	7	3*	16
3a (multiform VES)	5	26	5	31	8	53	4	21
3b (uniform + paired VES)	0	0	2	13	0	0	2	11
4 (multiform + paired VES)	13	68	8	50	3*	20	3**	16
5 (VT)	10	53	10	63	2***	13	1**	5

No. and %, number and percentage of patients, respectively; VES, ventricular extrasystoles; VT, ventricular tachycardia.

*p<0.025.

**p<0.01.

***p<0.05.

Table 4 Clinical and 72-hour ambulatory electrocardiographic findings in patients with ventricular tachycardia

Case no.	Rhythm	Maximum VES/h				Maximum VES/24 h				No. of beats in longest episode of VT (No. of episodes of VT)				Syncope	Family history	Dyspnoea NYHA	IVS (mm)	LVEDP	LVOT gradient
		B	V	A ^I	A ^m	B	V	A ^I	A ^m	B	V	A ^I	A ^m						
1	SR	36	—	7	1	63	—	18	2	25 (4)	—	0	0	Y	Negative	II	23	16	Resting
2	SR	17	—	2	1	78	—	2	2	4 (2)	—	0	0	N	Negative	II	25	20	Resting
3	SR	188	12	6	1	230	40	19	1	0	5 (1)	3 (1)	0	N	Negative	II	16	15	Labile
4	AF	37	26	16	19	300	342	135	73	27 (9)	8 (10)	5 (1)	0	N	HCM & SD	II	27	10	Resting
5	SR	203	110	10	53	1106	426	66	231	10 (6)	0	0	3 (1)	N	HCM & SD	II	30	10	Resting
6	SR	2	7	3	0	6	18	9	0	0	9 (3)	0	0	N	HCM	II	14	15	None
7	AF	50	27	—	59	546	184	—	828	9 (2)	7 (2)	—	0	Y	Negative	II	19	16	Resting
8	SR	68	38	2	7	729	265	8	127	7 (5)	10 (11)	0	0	N	Negative	II	18	10	None
9	SR	55	48	47	19	378	417	303	70	10 (2)	5 (3)	0	0	N	Negative	I	28	34	None
10	SR	3	1	1	0	5	15	2	1	0	18 (1)	0	0	N	Negative	II	—	15	Labile
11	SR	7	109	1	2	40	2074	2	2	4 (1)	5 (4)	0	0	N	HCM & SD	II	19	22	Resting
12	SR	51	37	—	7	300	187	—	15	6 (1)	7 (5)	—	0	N	Negative	II	16	20	Labile
13	SR	188	170	—	2	769	820	—	7	23 (35)	21 (27)	—	0	Y	Negative	I	16	15	None
Mean						350	435	56	105	(5.2)	(6.1)	<1	<1				21	17	
±SEM						± 96	178	30	63	±(2.8)	(2.4)	—	—				± 1.6	± 1.9	

SR, sinus rhythm; AF, atrial fibrillation; VES, ventricular extrasystole; VT, ventricular tachycardia; IVS, intraventricular septal thickness; LVEDP, mean left ventricular end-diastolic pressure; LVOT, left ventricular outflow tract; HCM, hypertrophic cardiomyopathy; SD, sudden death; NYHA, New York Heart Association classification; B, baseline; V, verapamil; A^l, amiodarone loading; A^m, amiodarone maintenance; —, not studied.

Table 5 Treadmill exercise in 12 patients with hypertrophic cardiomyopathy

	No treatment	Verapamil	Amiodarone loading dose	Amiodarone maintenance dose
Heart rate (beats/min)				
Resting	50–120	45–100	40–78	53–80
Mean	85	69*	61*	66*
Maximum	110–200	105–160	100–170	100–150
Mean	160	126**	131***	133***
Duration of exercise (min)	4.7–12.6	9.8–12.9	8.0–15.0	6.5–13.3
Mean	10.27	11.65	11.40	10.91
Arrhythmia (no. of patients)				
<1 VES/min	8	6	12	10
≥1 VES/min	3	1	0	1

VES, ventricular extrasystoles.

*p<0.001.

**p<0.002.

***p<0.01.

significantly reduced during amiodarone (less than 1) (p<0.001) (Table 4). The average daily number of ventricular extrasystoles off treatment (350) was unchanged on verapamil (435) but was significantly reduced during amiodarone (loading 56, p<0.001; maintenance 105, p<0.001).

During treadmill exercise testing (Table 5) the mean resting and maximum heart rates were significantly reduced on both verapamil and amiodarone. The mean duration of exercise, however, was similar during the four treatment periods. During maximal exercise one patient, who did not have ventricular tachycardia on ambulatory monitoring, developed this arrhythmia while on verapamil. In addition, 14 had uniform ventricular extrasystoles but none developed supraventricular tachycardia or more serious ventricular arrhythmias.

Discussion

Although symptoms may be severe, the most important clinical problem in hypertrophic cardiomyopathy is the prevention of sudden death: 30% of patients die suddenly before the age of 30.³ While beta-adrenergic blocking agents improve symptoms and are widely used they do not appear to have prevented sudden death.³ In our series, 23 of 32 patients who died suddenly had been taking propranolol (mean 240 mg daily) for at least three years.³

Recently verapamil had been advocated to improve symptoms, to increase exercise tolerance, and possibly to reverse myocardial hypertrophy.^{7–9} Verapamil is a slow channel blocker and its main electrophysiological action is on the atrioventricular node.¹⁷ Because after-depolarisations and triggered activa-

tions are suppressed by verapamil it has been suggested that some ventricular tachycardias might respond to it.¹⁸ The in vitro effects of verapamil on muscle thickness and arrhythmia provide an attractive theoretical basis for treatment in hypertrophic cardiomyopathy. These desirable antiarrhythmic effects were not, however, seen with this drug; seven of eight patients continued to have ventricular tachycardia and three further patients appeared to develop more ventricular arrhythmias on verapamil.

Although clinical studies suggest attenuation of the electrocardiographic⁹ and echocardiographic⁸ features of ventricular hypertrophy on verapamil, the natural history of ventricular hypertrophy in hypertrophic cardiomyopathy is variable and the relation of hypertrophy to sudden death is problematic. Of the patients who die suddenly many have massive myocardial hypertrophy,² but others have near-normal heart weights as well as near-normal echocardiographic indices of wall thickness.¹⁹ Serious ventricular arrhythmia is common⁴ and associated with sudden death;⁵ such arrhythmia is positively correlated with impaired septal motion but not with ventricular wall thickness.²⁰

What then are the important determinates of prognosis? Clinical manifestation of the disease in childhood,³ a family history of hypertrophic cardiomyopathy and sudden death,^{3, 19} rapidly progressive disease,³ and multiform and pairs of ventricular extrasystoles or ventricular tachycardia during electrocardiographic monitoring⁵ are associated with sudden death. The antiarrhythmic action of amiodarone appears to result from prolongation of the duration of the action potential.²¹ The electrophysiological action is seen as prolongation of refractoriness of both atrial and ventricular myocardium²²; so it seemed appropriate to investigate this aspect of its activity in hypertrophic cardiomyopathy. In 13 patients with refractory ventricular arrhythmia, we observed abolition of ventricular tachycardia after amiodarone in 10, and a significant reduction in the number of patients with either frequent or "high grade" ventricular extrasystoles. In addition three of the five patients who had longstanding atrial fibrillation reverted to and have remained in sinus rhythm. Regularisation of the heart rate and restoration of the contribution of atrial contraction to diastolic filling may be particularly beneficial in hypertrophic cardiomyopathy where diastolic filling may be a major determinant of systolic function.²³ Further studies to assess these haemodynamic effects of amiodarone therapy are needed and longer observation is required to determine whether suppression of ventricular arrhythmia with amiodarone will be maintained and if it will improve prognosis.

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