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Multicenter Study of the Efficacy and Safety of Disopyramide in Obstructive Hypertrophic Cardiomyopathy

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OBJECTIVES In this study we assessed the long-term efficacy and safety of disopyramide for patients with obstructive hypertrophic cardiomyopathy (HCM).

BACKGROUND It has been reported that disopyramide may reduce left ventricular outflow gradient and improve symptoms in patients with HCM. However, long-term efficacy and safety of disopyramide has not been shown in a large cohort.

METHODS Clinical and echocardiographic data were evaluated in 118 obstructive HCM patients treated with disopyramide at 4 HCM treatment centers. Mortality in the disopyramide-treated patients was compared with 373 obstructive HCM patients not treated with disopyramide.

RESULTS Patients were followed with disopyramide for 3.1 ± 2.6 years; dose 432 ± 181 mg/day (97% also received beta-blockers). Seventy-eight patients (66%) were maintained with disopyramide without the necessity for major non-pharmacologic intervention with surgical myectomy, alcohol ablation, or pacing; outflow gradient at rest decreased from 75 ± 33 to 40 ± 32 mm Hg ($p < 0.0001$) and mean New York Heart Association functional class from 2.3 ± 0.7 to 1.7 ± 0.6 ($p < 0.0001$). Forty other patients (34%) could not be satisfactorily managed with disopyramide and required major invasive interventions because of inadequate symptom and gradient control or vagolytic side effects. All-cause annual cardiac death rate between disopyramide and non–disopyramide-treated patients did not differ significantly, 1.4% versus 2.6%/year ($p = 0.07$). There was also no difference in sudden death rate, 1.0%/year versus 1.8%/year ($p = 0.08$).

CONCLUSIONS Two-thirds of obstructed HCM patients treated with disopyramide could be managed medically with amelioration of symptoms and about 50% reduction in subaortic gradient over ≥3 years. Disopyramide therapy does not appear to be proarrhythmic in HCM and should be considered before proceeding to surgical myectomy or alternate strategies. (J Am Coll Cardiol 2005;45:1251–8) © 2005 by the American College of Cardiology Foundation

Dynamic obstruction to left ventricular (LV) outflow due to systolic anterior motion of the mitral valve occurs at rest in 20% to 25% of patients with hypertrophic cardiomyopathy (HCM), and is associated with exercise intolerance due to dyspnea or angina, and with cardiovascular mortality (1–6). Traditionally, negative inotropic drugs represent the first-line treatment for symptomatic patients with obstructive HCM. Beta-blockers, often administered first, may improve symptoms, but generally do not reduce outflow gradient at rest (7–12). Verapamil has only a modest effect on outflow gradient and should be avoided in patients with particularly marked obstruction associated with severe symptoms (13,14).

Disopyramide, a type I antiarrhythmic drug, has considerable negative inotropic effects and represents a potential alternative drug regimen for obstructive HCM (2,12,15–25). However, the efficacy of disopyramide in ameliorating outflow gradient and heart failure symptoms has been reported only in relatively small short-term studies (16–25). Furthermore, determining the safety of disopyramide is particularly important, given the theoretic potential for proarrhythmia in this clinical setting (26) and recognition that the natural history of HCM may be complicated by malignant ventricular arrhythmias and sudden death (3,5,27,28). Therefore, in this study it is timely to report the clinical course of 118 patients with obstructive HCM treated with oral disopyramide.

METHODS

Patient selection. The study included all patients with obstructive HCM consecutively treated at four HCM centers from 1990 to 1999. These institutions maintain databases of all HCM patients evaluated, with regular periodic follow-up by either clinic visit or annual telephone interviews or questionnaires. In the 10-year time period there

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Abbreviations and Acronyms

Diso = disopyramide
ECG = electrocardiogram/electrocardiographic
HCM = hypertrophic cardiomyopathy
LV = left ventricle/ventricular
NYHA = New York Heart Association
SAM = systolic anterior motion

were 1,529 patients treated at the four participating centers. Of these patients, 491 (32%) had outflow obstruction at rest (gradient ≥30 mm Hg) and 118 (24%) were treated with disopyramide. The decision to initiate disopyramide for any individual patient was made by the treating physician at the respective HCM center. This was an integrated judgment based on symptoms, echocardiographic findings, and the patient response to previously administered cardioactive drugs (2,12). All patients enrolled at participating U.S. institutions consented to the use of their medical information for research purposes.

Follow-up began at the initial evaluation when patients presented for the first time to the respective HCM center. Data were collected about symptoms, gradient, and known risk factors for HCM mortality (3,5,27,28). Disopyramide controlled release was routinely initiated in a dose of 200 or 250 mg twice a day. Local practice patterns determined whether patients were admitted to the hospital for this purpose. In the U.S. centers and in Poland, disopyramide was initiated during a two-day hospitalization with electrocardiographic (ECG) monitoring (29). In the United Kingdom, disopyramide was initially administered in an outpatient setting (30). If symptoms did not improve, the dose was increased by increments of 100 mg per day at 2-week intervals, up to a maximum tolerated dose of usually 600 mg/day. Electrocardiograms were performed on all clinic visits during disopyramide therapy to monitor QT duration (3).

The most recent evaluation was performed by 2002. At that time in disopyramide-treated patients we recorded New York Heart Association (NYHA) functional class and the last echocardiographically measured outflow gradient performed while patients took medication. If patients underwent a major invasive non-pharmacologic intervention (e.g., surgical septal myectomy, alcohol septal ablation, or dual-chamber pacing), the last NYHA functional class and gradient measured before intervention was selected to assure that any change in symptoms or magnitude of obstruction could be attributed to a drug effect.

For the survival analyses, we compared mortality in the disopyramide-treated patients with all other 373 obstructed HCM patients treated at the same centers without disopyramide. Annual death rates were compared in the disopyramide-treated and non–disopyramide-treated groups. Characteristics of the two patient groups are shown in Table 1.

Mortality was classified as non-cardiac, non-sudden cardiac, and sudden cardiac death. Sudden cardiac death was defined as sudden collapse occurring <1 h from the onset of symptoms in patients without previous severe heart failure-related symptoms (including those patients successfully resuscitated from cardiac arrest). Non-sudden cardiac deaths occurred in the context of progressive dyspnea and exercise intolerance, often necessitating hospitalization. Patients requiring heart transplantation for severe progressive heart failure with LV systolic dysfunction were classified as non-sudden cardiac deaths. All-cause cardiac deaths were the sum of the sudden cardiac deaths plus the non-sudden cardiac deaths. In this study we did not attempt to classify whether a given cardiac death was due to HCM.

Table 1. Baseline Characteristics and Treatments in the Disopyramide- and Non–Disopyramide-Treated Patients

Number of patients	118	373	—
Age at initial evaluation (yrs)	47 ± 20	43 ± 21	0.1
Duration of follow-up (yrs)	4.2 ± 2.9	6.5 ± 5.2	<0.001
Age at last evaluation (yrs)	51 ± 20	50 ± 21	0.7
Male gender (%)	51	53	0.8
NYHA functional class at initial evaluation	2.3 ± 0.7	1.9 ± 0.8	<0.002
Syncope or pre-syncope (%)	47	26	<0.001
Dyspnea (%)	82	60	<0.001
NSVT (%)	18	17	0.7
Family history of SCD (%)	15	15	0.9
AF at initial evaluation (%)*	20	18	0.7
AF during follow-up (%)*	14	17	0.3
LV outflow gradient (mm Hg)	74 ± 35	62 ± 32	<0.002
Max LV thickness (mm)	21.9 ± 5.5	23.7 ± 6.4	<0.02
Coronary stenosis >70% (%)	7	2	<0.02
Beta-blocker (%)	98	70	<0.001
Calcium channel blocker (%)	32	27	0.2
Amiodarone (%)	10	30	<0.001
Septal myectomy (%)	19	9	0.01
Alcohol septal ablation (%)	9	9	1
DDD pacemaker (%)†	11	14	0.4
All interventions combined (%)	34	28	0.2
ICD (%)‡	5	2	0.3
Stroke during follow-up (%)	3	2	0.6§

*Clinically overt atrial fibrillation requiring treatment; †one additional patient had asymptomatic intermittent type II second-degree AV block nine years after beginning disopyramide; a pacemaker was implanted and disopyramide continued; ‡no appropriate ICD shocks at time of follow-up in either group; §Fisher exact test.

AF = atrial fibrillation; AV = atrioventricular; DDD = dual chamber; ICD = implantable cardioverter-defibrillator; LV = left ventricular; Max = maximum; NSVT = nonsustained ventricular tachycardia; NYHA = New York Heart Association; SCD = sudden cardiac death.

Echocardiography. Hypertrophic cardiomyopathy was diagnosed on the basis of two-dimensional echocardiographic demonstration of a hypertrophied (wall thickness ≥15 mm) and non-dilated LV in the absence of another cardiac or systemic disease capable of producing the magnitude of hypertrophy evident (3,5). Maximum LV wall thickness was assessed from the two-dimensional echocardiogram as previously described (31). Continuous-wave Doppler was used to measure LV outflow gradient (32). Left ventricular outflow obstruction was defined as a peak instantaneous gradient under basal (resting) conditions ≥30 mm Hg attributable to systolic anterior motion (SAM) of the mitral valve.

Statistics. Paired and unpaired Student *t* tests were used to compare continuous variables. For categorical variables we