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
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.

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
used chi-square tests when all cell expectations were >5; otherwise, Fisher exact tests were used. Annualized mortality rates, beginning after initial evaluation at each participating HCM treatment center were calculated by the person-year method as the number of patients who died divided by the years of follow-up. Kaplan-Meier estimates were used to model survival rates for all-cause cardiac, sudden death, and total mortality. The Wilcoxon (Gehan-Breslow) test compared survival rates between groups.

Hazard ratios for death while taking disopyramide were calculated from proportional hazard regression models assuming constant hazard rate. Adjusted hazard ratios for all-cause cardiac death while taking disopyramide were calculated from proportional hazard regression models assuming constant hazard rate, entering as covariates age at initial evaluation, treatments with surgical septal myectomy, beta-blockers, calcium channel blockers, and amiodarone as well as maximum LV wall thickness. SPSS 10.1 (SPSS Inc., Chicago, Illinois) and SAS 8.2 software (SAS Institute Inc., Cary, North Carolina) were used for statistical analyses.

RESULTS

Baseline characteristics. At initial evaluation the 118 study patients treated with disopyramide at four centers were 47 ± 20 years of age (range 1 month to 94 years); 60 (51%) were male. Left ventricular outflow gradient at rest was 74 ± 35 mm Hg (range 30 to 185 mm Hg). New York Heart Association functional class was 2.3 ± 0.7; 14 (12%) currently had normal exercise tolerance in class I, 59 (50%) were mildly symptomatic in class II, and 45 (38%) were severely symptomatic in classes III and IV. Exertional dyspnea and syncope or pre-syncope were the most frequent symptoms occurring in 97 (82%) and 55 (47%) of the patients, respectively. Disopyramide was administered to the 14 patients in NYHA functional class I because of high resting gradients associated with episodes of impaired consciousness (including syncope in 8 patients) judged to be probably due to outflow obstruction.

Clinical course of disopyramide patients. Of the 118 disopyramide patients, 108 (92%) began with disopyramide 8 ± 17 months (range 0.1 to 82 months) after initial evaluation, whereas 10 (8%) had started with disopyramide 28 ± 36 months (range 2 to 100 months) previously. Duration of follow-up from initial evaluation was 4.2 ± 2.9 years during which patients received disopyramide for 3.1 ± 2.6 years (range 0.2 to 18 years). Clinical follow-up was complete in all 118 patients in the disopyramide group through either clinic visit or phone interview.

Before the initial evaluation 70 (59%) patients had received beta-blockers, 35 (30%) had received calcium channel blockers, and 11 (9%) had received a trial of both. Eleven (9%) had received another anti-arrhythmic besides disopyramide before initial evaluation. Highest dose of administered disopyramide was 432 ± 181 mg/day (range 150 to 900 mg/day). In addition, 115 (97%) patients received a beta-blocker during follow-up on disopyramide.

Patients taking disopyramide without major intervention. Of the 118 disopyramide patients, 78 (66%) were successfully managed medically with disopyramide and did not require major interventions (e.g., surgical septal myectomy, alcohol septal ablation, or dual-chamber pacing) over 3.3 ± 2.7 years. In patients who were treated medically with disopyramide and a beta-blocker, and who did not require a major invasive intervention during follow-up, average peak outflow gradient decreased substantially from 75 ± 33 to 40 ± 32 mm Hg (p < 0.0001) (Fig. 1).

Mean NYHA functional class score decreased from 2.3 ± 0.7 to 1.7 ± 0.6 (p < 0.0001) (Fig. 2). At initial evaluation distribution of NYHA functional class was I = 9; II = 40; III/IV = 29, and at follow-up distribution was I = 29; II = 42, III/IV = 7 (p < 0.001).

Patients requiring non-pharmacologic major interventions. The other 40 disopyramide-treated patients (34%) required interventions 2.0 ± 2.1 years after beginning drug therapy because of both inadequate symptom control and persistent gradients ≥50 mm Hg (n = 29), or because of drug intolerance (n = 8) or withdrawal due to initiation of amiodarone (n = 3). Of the eight patients with disopyramide intolerance, five had the drug terminated due to dry mouth and three because of symptoms related to prostatism. Interventions were 22 surgical septal myectomies, 10 alcohol septal ablations, and 8 dual-chamber pacemakers. In patients who required an invasive intervention to control outflow gradient and heart failure symptoms, average peak gradient decreased modestly from 73 ± 35 to 63 ± 31 mm Hg (p = 0.05) (Fig. 1, right panel). These patients had higher gradients while taking disopyramide than did those not requiring intervention, 63 ± 31 mm Hg versus 40 ± 32 mm Hg (p = 0.001) (Fig. 1). In these patients there was no improvement in NYHA functional class when comparing symptoms before and after disopyramide, 2.3 ± 0.7 versus 2.3 ± 0.6 (p = 0.6) (Fig. 2). Those patients requiring interventions had a higher NYHA functional class at last evaluation than did those not requiring intervention, 2.3 ± 0.6 vs. 1.7 ± 0.6 (p < 0.0001).

Disopyramide patients treated medically without intervention and those who required invasive intervention did not differ significantly with regard to baseline characteristics: outflow gradient 72 ± 35 mm Hg versus 78 ± 38 mm Hg (p = 0.4); maximal LV wall thickness 21.1 ± 5 mm versus 23.1 ± 6 mm (p = 0.08); NYHA functional class, 2.3 ± 0.7 versus 2.3 ± 0.7 (p = 0.9); age, 48 ± 20 years versus 44 ± 20 years (p = 0.2); gender 44% versus 55% female (p = 0.24); disopyramide dose 425 ± 169 mg/day versus 445 ± 201 mg/day (p = 0.6).

Sudden deaths in disopyramide-treated patients. Over the follow-up period there were four sudden cardiac deaths in patients who were taking disopyramide at the time. One other death occurred nine months after withdrawal of disopyramide while the patient was taking a beta-blocker.
The four deaths occurred at 46 ± 13 years of age (range 27 to 55 years), 54 ± 43 months (range 2.5 to 98 months) after disopyramide was initiated. Annual sudden death rate while actually taking disopyramide was 0.8%/year. By intention-to-treat principle annual sudden death rate in patients begun with disopyramide was 1.0%/year.

Patients with and without sudden death while actually taking disopyramide did not differ with respect to age, 41 ± 15 years versus 47 ± 20 years (p = 0.5); NYHA functional class, 2.0 ± 0.8 versus 2.3 ± 0.7 (p = 0.4); gradient, 88 ± 35 mm Hg versus 74 ± 35 mm Hg (p = 0.4); or disopyramide dose, 517 ± 225 mg versus 424 ± 171 mg (p = 0.4).

Survival analysis. There was no significant difference the in annualized all-cause cardiac death rate, 1.4% versus 2.6%/year (p = 0.07), between the 118 disopyramide-treated and 373 non-disopyramide-treated HCM patients. There was also no difference in the annualized sudden death rate, 1.0%/year versus 1.8%/year (p = 0.08) (Table 2, Figs. 3 and 4). There also was no significant difference in annualized total mortality between the disopyramide-treated and non-disopyramide-treated patients, 2.8% versus

Table 2. Annualized Death Rates in Disopyramide- and Non-Disopyramide-Treated Patients

<table>
<thead>
<tr>
<th>Mode of Death</th>
<th>Disopyramide</th>
<th>Non-Disopyramide</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-cardiac</td>
<td>1.4%</td>
<td>1.2%</td>
<td>0.75</td>
</tr>
<tr>
<td>Non-sudden cardiac</td>
<td>0.4%</td>
<td>0.9%</td>
<td>0.54</td>
</tr>
<tr>
<td>Sudden cardiac</td>
<td>1.0%</td>
<td>1.8%</td>
<td>0.08</td>
</tr>
<tr>
<td>All-cause cardiac</td>
<td>1.4%</td>
<td>2.6%</td>
<td>0.07</td>
</tr>
<tr>
<td>All deaths</td>
<td>2.8%</td>
<td>3.8%</td>
<td>0.1</td>
</tr>
</tbody>
</table>

Figure 1. (Left) Response of peak instantaneous systolic left ventricular outflow tract gradient in patients treated medically with disopyramide (Diso) without the requirement for invasive non-pharmacologic intervention (such as surgical septal myectomy, alcohol septal ablation, or dual-chamber pacing). Depicted are the outflow gradients of 62 patients who had serial echocardiographic assessments with continuous-wave Doppler. (Right) Patients who required invasive intervention because of inadequate relief of heart failure symptoms and persistent outflow gradients. Depicted are the outflow gradients of 33 patients who had serial echocardiographic assessments. All gradient measurements in this group were performed before intervention.

Figure 2. Response of New York Heart Association (NYHA) functional class in patients treated medically with disopyramide (Diso) but without requirement for invasive non-pharmacologic intervention (such as surgical septal myectomy, alcohol septal ablation, or dual-chamber pacing), and in patients with failed maximum medical therapy who ultimately did require such interventions.
3.8%/year (p = 0.1). Hazard ratio for all-cause cardiac death while taking disopyramide was 0.55 (confidence interval = 0.24 to 1.20; p = 0.13).

There was no difference in the frequency of atrial fibrillation and stroke in the two groups (Table 1). There were no appropriate discharges of implantable cardioverter-defibrillators in either the disopyramide or control groups, but two deaths related to surgical septal myectomy occurred in the non-disopyramide-treated patients.

With multivariate analysis that included treatment with surgical septal myectomy, beta-blockers, calcium channel blockers or amiodarone, maximum LV wall thickness, and age, the hazard ratio for all-cause cardiac death on disopyramide still showed no significant difference between the
disopyramide and non-disopyramide comparison group, with a hazard ratio of 0.72 (confidence interval = 0.32 to 1.64; \( p = 0.43 \)).

DISCUSSION

Drug benefit. The present study substantiates that pharmacologic therapy in obstructive HCM can be successful in controlling heart failure symptoms in most patients, and that disopyramide (in combination with a beta-blocker) has a role in the maximal medical management of this disease by virtue of sustained reduction of outflow gradient and disabling symptoms in two-thirds of study patients. Average peak LV outflow gradient at rest was reduced after three years by almost 50% and generally below the threshold at which surgery would be considered. Limiting symptoms improved in parallel, with the mean NYHA functional class decreasing from 2.3 to 1.7. Indeed, two-thirds of our patients have had gratifying results and did not require invasive intervention, largely because of disopyramide, for more than three years.

The remaining one-third of our patients were non-responders and accrued no sustained pharmacologic benefit. Disopyramide was ineffective in controlling symptoms and gradient, or vagolytic side effects required discontinuation of the drug. In these latter treatment failures a major non-pharmacologic intervention (e.g., surgical septal myectomy, alcohol septal ablation, or dual-chamber pacing) was required an average of two years after disopyramide was initiated.

Mortality analysis. Disopyramide-treated HCM patients were compared with a group of obstructive HCM patients with a similar degree of outflow obstruction treated without disopyramide at the four centers. There was no difference in annualized all-cause cardiac death rates, 1.4%/year versus 2.6%/year, between disopyramide-treated and the non-disopyramide-treated patients, and also no difference in sudden cardiac death rates in these two groups, 1.0%/year versus 1.8%/year. This analysis substantiates that disopyramide is not proarrhythmic in HCM and does not increase the risk for sudden or other cardiac death. The lack of a significant difference between the disopyramide and comparison groups persisted after multivariate analysis, which included as covariates surgical myectomy, drug therapy with beta-blockers, calcium channel blockers, and amiodarone, maximum LV wall thickness, and age.

Mechanism of disopyramide benefit. The mechanism of disopyramide benefit for outflow gradient and symptom relief in HCM is likely attributable to its negative inotropic effects (15,20,33). After disopyramide, LV ejection fraction has been reported to decrease by 5% to 10% (23,34). The benefit for reduction of SAM and gradient appears to be mediated by a decrease in LV ejection acceleration (20). By decreasing ejection velocities early in systole, negative inotropic drugs decrease hydrodynamic forces on the mitral valve, thus delaying or preventing SAM. Drag, the pushing force of flow, appears to be the predominant hydrodynamic force on the mitral leaflets (4,35–37). Because this hydrodynamic force on the leaflet is proportional to the square of the velocity, even small changes in acceleration and velocity can lead to large decreases in force (20,37). Lowering gradients may benefit symptoms by a variety of mechanisms including improvement in oxygen supply-demand mismatch, LV relaxation by relieving systolic load, and LV ejection flow (18,23,38–41).

Role of disopyramide for symptomatic obstructive HCM. Symptomatic HCM patients with outflow obstruction are generally treated initially with a beta-blocker, which may blunt gradients that are physiologically provoked with exercise and thereby improve symptoms. However, beta-blocking therapy is not expected to reduce resting gradient (7–12) and may not control symptoms satisfactorily in some patients. For those patients with refractory obstruction and symptoms after a trial with beta-blockers, alternative drugs are required. There has been diversity in the selection of the second drug trial. The most frequent approach is to substitute verapamil for beta-blocker (13,42–44). Others support an alternate strategy of combining disopyramide with a beta-blocker (2,12,20,45).

Previous studies using verapamil in symptomatic obstructed HCM patients have showed relatively frequent cardiac hemodynamic and electrophysiologic side effects early after institution of the drug (13,14,42,44). Patients who developed severe pulmonary congestion usually had substantial pre-existing heart failure symptoms, high pulmonary wedge pressures, and LV outflow gradients exceeding 50 mm Hg (14,42). This is a potentially important limitation given the intuition to administer verapamil to medically refractory patients who would otherwise be candidates for septal myectomy or other interventions. Therefore, some investigators reserve verapamil for those patients with mild or moderate symptoms and no or modest outflow gradients (1,2,12,45).

The present study of disopyramide appears to contrast with the experience using verapamil in obstructive HCM (13,14,42). In the first six months of disopyramide therapy only one patient developed worsening heart failure apparently due to disease progression. This low incidence is likely attributable to the recognition that disopyramide is not associated with vasodilation (16,18). Furthermore, our only experience with bradycardia or atrio-ventricular block (not uncommon with verapamil) was in a patient after nine years of disopyramide treatment. The principal side effects of disopyramide were the vagolytic effects of dry mouth and prostatism that caused drug discontinuation relatively infrequently in 7% of our patients. Disopyramide generally does not cause hepatic, renal, or central nervous system toxicity, and none was observed in the present study.

Kimball et al. (21) noted a modest 5% increase in corrected QT interval from 423 to 443 ms in HCM patients treated with disopyramide, which was similar to that observed previously in normal subjects (46). In the present
study, ECG surveillance was routinely performed on all clinic follow-up visits as recommended (3); marked QT interval prolongation was not identified and the drug was not discontinued in any patient for this reason.

**Study limitations.** Despite the retrospective design of this study, we believe that our observations regarding disopyramide efficacy and safety can be regarded as representative. For example, the lack of significant difference in mortality between the disopyramide and non-disopyramide patients is substantiated for a number of reasons. First, disopyramide-treated patients had higher outflow gradients and were more symptomatic than the comparison group of HCM patients and, therefore, could be expected to have less favorable outcome. Second, disopyramide and non-disopyramide patients were similar with respect to their risk factors for HCM-related mortality. Third, the lack of difference in all-cause cardiac mortality with disopyramide persisted after multivariate analysis that included other treatment modalities as covariates.

Of note, only about 5% of our patients could not tolerate disopyramide and required premature termination of the drug. However, it is important to emphasize that disopyramide should not be administered to HCM patients in certain clinical scenarios, such as when prostatism is present. Other antiarrhythmic drugs such as amiodarone or sotalol should not be administered in association with disopyramide in order to avoid possible proarrhythmia. If such agents are to be used, disopyramide should be discontinued. Because of its impaired elimination in patients with renal insufficiency, disopyramide should be administered in reduced dosage and with careful monitoring in such patients (17). Because there was no direct comparison of disopyramide with other cardioactive agents in this study design, we cannot conclude from our data that one pharmacologic agent was superior to another in the treatment of symptoms in HCM.

**Conclusions.** Disopyramide has a useful role in the therapeutic armamentarium for obstructive HCM by virtue of reducing LV outflow tract gradients and controlling symptoms in the majority of patients. Disopyramide does not appear to be proarrhythmic in HCM. Administration of disopyramide, in combination with a beta-blocker, should be considered in patients with obstructive HCM before proceeding to invasive interventions.

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