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Short communication

Disopyramide is a safe and effective treatment for children with obstructive hypertrophic cardiomyopathy

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ABSTRACT

Background: Left ventricular outflow tract obstruction (LVOTO) is present in 1/3 of children with Hypertrophic Cardiomyopathy (HCM). Disopyramide improves symptoms associated with LVOTO and delays surgical intervention in adults, but it is not licensed in children.

Aim: To describe a single-centre thirty-year experience of using disopyramide to treat LVOTO-related symptoms in a paediatric HCM cohort.

Methods: Clinical data were collected for all patients meeting diagnostic criteria for HCM (<18 years) at the time of initiation, 6 months after, and last follow-up or end of disopyramide treatment. It included demographics, clinical history, 12-lead electrocardiography, and echocardiography. Comparisons between baseline and 6 month follow up, and end of follow up respectively were performed.

Results: Fifty-one patients with HCM were started on disopyramide at a mean age 10.2±5.3 years. At 6 months, of those previously symptomatic, 33(86.8%) reported an improvement of symptoms and 12(31.6%) were asymptomatic. PR interval, corrected QT interval and maximal LVOT gradient had not significantly changed, but fewer participants were noted to have systolic anterior motion of the mitral valve 31 (72.1%) vs. 26 (57.80%). Patients were followed up for a median of 1.9 years (IQR 0.83–4.5). Nine patients (17.6%) reported side effects, and eleven patients (33.3%) with initial improvement in symptoms reported a return or worsening of symptoms requiring a change in medication ($n = 4$, 12.1%) or left ventricular septal myomectomy ($n = 7$, 21.2%) during follow up.

Conclusion: Disopyramide is a safe and effective treatment for LVOTO-related symptoms in childhood obstructive HCM. Any delay in the need for invasive intervention, particularly during childhood, is of clear clinical benefit.

1. Introduction

Left ventricular outflow tract obstruction (LVOTO) is present at rest in up to one third of children with Hypertrophic Cardiomyopathy (HCM), with a further 50–60% of symptomatic children reported to develop a gradient on exertion [1,2]. First-line management of symptoms attributable to LVOTO is medical therapy, with surgical intervention for those in whom medical therapy fails. Disopyramide has been shown to improve symptoms and reduce the need for surgical intervention in adult patients [3]. However, it is not licensed for use in children and data supporting its use in younger patients are more limited [4,5]. This study describes a single-centre thirty-year experience of using disopyramide to treat LVOTO-related symptoms in a paediatric HCM cohort.

2. Methods

2.1. Ethical approval

The study received ethical approval from Great Ormond Street Hospital research office.

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2.2. Study population

The study cohort consisted of participants meeting the diagnostic criteria for HCM aged 18 or younger recruited at the Great Ormond Street Hospital [6] between 1994 and 2021.

2.3. Data collection

Anonymised, non-invasive clinical data were collected for all study participants at (1) time of initiation, (2) 6 months after, and (3) last follow-up or end of disopyramide treatment. Collected data included demographics, HCM clinical history, disopyramide medication history, 12-lead electrocardiography (ECG) which provided corrected QT interval using Bazett's formula (ms) and 2D Doppler and colour transthoracic echocardiography which provided maximal resting LVOT (mmHg). For the duration of the study, disopyramide was used as second line medical therapy for LVOTO related symptoms (usually after β-blockers or calcium channel blockers), with surgical septal reduction therapy reserved for those with treatment-resistant symptoms. Symptoms were recorded at the time of clinical assessment by the treating cardiologist.

2.4. Data analysis

Distribution of data was assessed on histograms, and normality checks were assessed by the Shapiro-Wilk test. Continuous variables were expressed as mean ± standard deviation if normally distributed or median (interquartile range, IQR) otherwise. Categorical variables were expressed as counts and percentages. Comparisons between baseline and 6 month follow up, and baseline and end of follow up were performed. Paired student's *t*-test was employed for comparisons between normally distributed variables, Wilcoxon rank-sum test was used for comparing skewed data, while Chi-squared test was used for comparing categorical variables.

3. Results

Fifty-one patients with HCM (Sarcomeric $n = 18$, 36%; RASopathy syndrome $n = 12$ (24%); inborn errors of metabolism $n = 2$, 4%; unknown aetiology $n = 19$, 37%) were started on disopyramide at a mean age 10.2 years (SD +/− 5.3). At initiation, the median daily dose of disopyramide was 100 mg (range 16 mg to 500 mg). Indication for treatment was self-reported LVOTO-related symptoms in 38 patients (74.5%) [shortness of breath ($n = 27$, 52.9%), chest pain ($n = 25$, 49.0%) and pre-syncope/syncope ($n = 16$, 31.4%)] and asymptomatic LVOTO in 6 (11.8%). Forty-nine patients (96.1%) were already established on

Table 1
Clinical phenotype at the time of disopyramide initiation and during follow up.

		Initiation	6 months follow up	P value^	End of follow up	P value ~
Demographics at baseline						
Sex, male (%)	34/51 (66.7)					
Age at diagnosis, years (mean, sd,n)	5.43 ± 5.34 [$n = 51$]					
Age at initiation, years (mean, sd,n)	10.22 ± 5.28 [n = 51]					
Symptoms						
Any symptoms (%)		38/51 (74.5%)	26/47 (55.3%)	**0.0462**	38/50 (76.0%)	**0.862**
NYHA class (%)	I	13/40 (32.5%)	16/41 (39.0%)	**<0.0001**	24/49 (49.0%)	**<0.0001**
	II	23/40 (57.5%)	21/41 (51.2%)		21/49 (42.9%)	
	III/IV	4/40 (10.0%)	4/41 (9.8%)		4/49 (8.2%)	
Chest pain (%)		25/51 (49.0%)	11/51(21.6%)	**<0.0001**	10/51(20.0%)	**<0.0001**
Dyspnoea (%)		25/51 (49.0%)	8/51 (15.7%)		6/51 (11.8%)	
Palpitations (%)		8/51 (15.7%)	6/51 (11.8%)		4/51 (7.8%)	
Pre−/syncope (%)		16/51(31.4%)	21/51(41.2%)		15/51(29.4%)	
Electrocardiography						
PR, ms (median, IQR, n)		141.0 (126.0, 160.0) [$n = 32$]	151.0 (132.5, 167.5) [$n = 34$]	0.403	156.0 (134.0, 165.0) [$n = 39$]	0.202
QTc, ms (median, IQR, n)		450.5 (438.8, 464.8) [n = 32]	452.5 (440, 479.3) [n = 34]	0.297	460 (440.0,479.0) [n = 39]	0.367
	QTc ≥ 500 ms (%)	3/41 (7.3%)	3/40 (7.5%)	0.975	5/29 (17.2%)	0.279
Echocardiography						
Maximal resting LVOT gradient, mmHg (median, IQR, n)		61.0 (25.0, 96.0) [n = 39]	49.5 (16.4, 79.3) [$n = 42$]	0.624	47.6 (11.0, 80.0) [$n = 46$]	0.215
	LVOT gradient ≥30 mmHg	28/39 (71.8%)	25/42 (59.5%)	0.246	27/46 (58.7%)	0.208
	LVOT gradient ≥50 mmHg	22/39 (56.4%)	21/42 (50.0%)	0.564	22/46 (47.8%)	0.430
LV MWT, mm (median, IQR, n)		20.0 (16.5, 23.1) [$n = 43$]	20.5 (16.0, 24.3) [$n = 44$]	0.969	21.0 (16.5, 25.5) [$n = 47$]	0.851
Systolic anterior motion of mitral valve (%)		31/43 (72.09)	26/45 (57.8)	**<0.0001**	27/46 (57.7)	**<0.0001**

Categorical results are reported as counts/total available (percentage), non-normally distributed variables are presented as median (interquartile range) and approximatively normally distributed variables are reported as mean ± standard deviation. Wilcoxon rank-sum test was used for comparing non-normally distributed variables, while Chi-squared test was used for comparing categorical variables.

^ p value represents comparison between baseline and 6 month follow up.

~ *p* value represents comparison between baseline and end of follow up.

HCM, hypertrophic cardiomyopathy; IQR, interquartile range; LVOT, left ventricular outflow tract; LV MWT, left ventricular maximal wall thickness; NYHA, New York Heart Association; QT_c, corrected QT interval; sd, standard deviation.

other cardioactive medications [B Blockers $n = 45$ (88.2%); calcium channel blockers $n = 3$ (5.9%); diuretics $n = 2$ (3.9%) and ivabradine $n = 1$ (2.0%)]. Clinical phenotype at treatment initiation and during follow up is shown in Table 1. At 6 months' follow-up, of those previously symptomatic, 33 (86.8%) reported an improvement of symptoms and 12 (31.6%) were asymptomatic. There was no significant difference in response to therapy between different HCM aetiologies [improvement in symptoms reported in 11/15 with sarcomeric HCM (73.3%) Vs 5/8 (62.5%) with non-sarcomeric HCM, p value 0.591]. PR interval, corrected QT interval and maximal LVOT gradient had not significantly changed (Table 1). However, fewer participants were noted to have systolic anterior motion of the mitral valve [$n = 31/43$ (72.1%) vs. $n = 26/45$ (57.80%) $p < 0.0001$] at 6 months and at the end of follow-up. Patients were followed up for a median of 1.9 years (IQR 0.83–4.5). Twenty-five (49.0%) remained on disopyramide at last clinical review. Nine patients (17.6%) reported side effects [antimuscarinic $n = 3$ (5.9%); fatigue n = 3 (5.9%); and QT prolongation >500 ms in $n = 2$ (3.9%)] leading to discontinuation of therapy in 7 (13.7%), of which 6 occurred within 6 months of starting treatment. While on disopyramide, one patient developed supraventricular tachycardia, another one ventricular bigeminy and trigeminy, and another had a sudden cardiac death. Eleven patients (33.3%) with initial improvement in symptoms reported a return or worsening of symptoms (chest pain $n = 6$, Exertional dyspnoea $n = 5$ and pre-syncope/syncope $n = 4$) requiring a change in medication (n = 4, 12.1%) or left ventricular septal myomectomy ($n = 7$, 21.2%) during follow up. Of patients undergoing surgical relief, 3 had developed fixed left-ventricular outflow tract obstruction.

4. Discussion

This study describes the largest experience to date of using disopyramide in childhood obstructive HCM [4,5]. Disopyramide treatment was associated with a significant reduction in self-reported symptoms at 6 months, most notably dyspnoea and chest pain, showing it to be a useful adjunct to beta-blockers even in the very young. Despite initial symptomatic improvement, there was no significant reduction in measured LVOT gradient at rest. LVOT gradient is recognized to be dynamic and varies depending on the haemodynamic state. Nonetheless, this is in contrast to adult cohorts [3] and could be explained by failure to elicit a maximal gradient in the absence of routine exercise provocation in young patients or reflect the underlying multifactorial aetiology of many symptoms in HCM, which includes LVOTO, ischaemia, arrhythmia or diastolic dysfunction. However, this finding supports the notion that treatment should be guided by symptoms and not for the purpose of gradient reduction alone. Overall, disopyramide was well tolerated but side effects were reported in 18% necessitating discontinuation of therapy in 14%. Although the proportion of patients reporting side effects was higher than described in adult series, a low proportion of patients (6%) reported antimuscarinic side effects, which is the main reason for discontinuing therapy in adult patients [3]. Disopyramide can be pro-arrhythmic due to its PR and QT prolonging effect yet, in common with previous adult studies [3], for the majority of childhood patients, therapy was not associated with a significant change in the PR or QT intervals. Although supraventricular and ventricular arrhythmias were reported in 3 individuals on disopyramide, it is not possible to determine whether this was incidental or causal. For the 2 patients in whom QT prolongation was seen, this occurred within 6 months of disopyramide initiation. On longer term follow up, symptomatic improvement was not sustained for one third of patients necessitating additional medical therapy or surgical myectomy for refractory symptoms. This could be explained by disease progression (for example the development of fixed LVOTO) or medication tachyphylaxis, which is a recognized phenomenon with disopyramide in adults, but could also represent an initial 'placebo effect' of disopyramide therapy. Nonetheless, any delay in the need for invasive intervention, particularly during childhood, is of clear clinical benefit.

The main limitation of this cohort study is its retrospective nature meaning it cannot be used to infer causality. Moreover, the symptoms were self-reported, and no validated tool was used to assess symptoms severity and exercise capacity, given the retrospective nature of the study. In contrast to other studies [4], disopyramide did not affect the maximal resting LVOT gradient meaning that the improvement in symptoms cannot be clearly attributed to the haemodynamic effect of the drug. However, a reduction in SAM of the mitral valve was observed at both 6 months and at the end of the follow-up, suggesting some effect of disopyramide on the mechanism of LVOTO.

5. Conclusion

This study suggests that disopyramide is a safe and effective treatment for LVOTO-related symptoms in childhood obstructive HCM. Future prospective studies would be useful to identify those most likely to benefit from treatment in this patient group.

Disclosure statement

The authors have nothing to disclose.

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