

Effect of Perindopril on the Onset and Progression of Left Ventricular Dysfunction in Duchenne Muscular Dystrophy

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| OBJECTIVES | The aim of this research was to examine the effects of perindopril on cardiac function in patients with Duchenne muscular dystrophy (DMD). |
| BACKGROUND | Duchenne muscular dystrophy, an inherited X-linked disease, is characterized by progressive muscle weakness and myocardial involvement. |
| METHODS | In phase I, 57 children with DMD and a left ventricular ejection fraction (LVEF) >55% (mean $65.0 \pm 5.4\%$), 9.5 to 13 years of age (mean 10.7 ± 1.2 years), were enrolled in a three-year multicenter, randomized, double-blind trial of perindopril, 2 to 4 mg/day (group 1), versus placebo (group 2). In phase II, all patients received open-label perindopril for 24 more months; LVEF was measured at 0, 36, and 60 months. |
| RESULTS | Phase I was completed by 56 (27 in group 1 and 29 in group 2) and phase II by 51 patients (24 in group 1 and 27 in group 2). There was no difference in baseline characteristics between the treatment groups. At the end of phase I, mean LVEF was $60.7 \pm 7.6\%$ in group 1 versus $64.4 \pm 9.8\%$ in group 2, and was <45% in a single patient in each group ($p = \text{NS}$). At 60 months, LVEF was $58.6 \pm 8.1\%$ in group 1 versus $56.0 \pm 15.5\%$ in group 2 ($p = \text{NS}$). A single patient had an LVEF <45% in group 1 versus eight patients in group 2 ($p = 0.02$). |
| CONCLUSIONS | Early treatment with perindopril delayed the onset and progression of prominent left ventricle dysfunction in children with DMD. (J Am Coll Cardiol 2005;45:855-7) © 2005 by the American College of Cardiology Foundation |

Duchenne muscular dystrophy (DMD), an inherited X-linked disease associated with absence of dystrophin (1), is characterized by progressive muscle weakness and inescapable cardiac involvement (1,2), fatal in approximately 40% of patients (3,4). Angiotensin-converting enzyme inhibitors (ACEI) are effective in overt congestive heart failure (CHF) (5) and have prophylactic effects in the Syrian hamster, an experimental model of beta-sarcoglycanopathy phenotypically similar to DMD (6,7).

See page 858

This study examined the preventive effects of the ACEI, perindopril, on the onset and progression of left ventricular (LV) dysfunction in children with DMD and a normal left ventricular ejection fraction (LVEF).

METHODS

This study was approved by the appropriate ethical review committees, and informed written consent was granted by the parents or legal guardians of all patients. Children between the ages of 9.5 and 13 years with genetically proven DMD, normal cardiac examination, and a radionuclide

LVEF >55% were included in the study provided they: 1) tolerated a 1-mg test dose of perindopril; and 2) had a systolic blood pressure ≥ 80 mm Hg in the supine or >70 mm Hg in the sitting position. Patients treated with cardioactive drugs, or with a blood urea nitrogen >7 mmol/l, or contraindications to ACEI therapy were not included.

Study protocol. This two-phase study was conducted at 10 medical institutions (Appendix). In a double-blind phase I, patients were randomly assigned to perindopril 2 to 4 mg daily as tolerated (group 1), or equivalent placebo (group 2), for three years. In phase II, both groups were treated with open-label perindopril, 2 to 4 mg daily, for two additional years. Other cardioactive medications were allowed in phase II, if indicated.

Outcome measures. All patients underwent detailed, serial, clinical, and drug tolerance evaluations, and routine laboratory screens. Resting radionuclide ventriculography was performed at baseline, 36 months, and 60 months, after *in vitro* erythrocyte labeling with 500 to 740 MBq technetium-99m, and analyzed in the nuclear medicine department of Cochin Hospital's core laboratory by two experts blinded to other study data.

The primary study end points were a reduction in mean LVEF, and in the number of patients whose LVEF fell below 45%. The cut-off value of 45% was predefined on the basis of prior studies where an LVEF <40% was an important prognostic factor in adults (8), and on the basis of a normal LVEF 5% higher in children than in adults in our

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Abbreviations and Acronyms

ACEI = angiotensin-converting enzyme inhibitors
CHF = congestive heart failure
DMD = Duchenne muscular dystrophy
LV = left ventricle/ventricular
LVEF = left ventricular ejection fraction

laboratory. Clinical data and tolerance of study drug were secondary end points.

Statistical analyses. Data, expressed as means ± SD, were analyzed according to the intention-to-treat principle, and LVEF measurements available were included in the analysis at each time point. Student *t* tests were used for normally distributed continuous variables, and chi-square analysis for differences in frequencies (*p* value <0.05 for significance).

RESULTS

Among 80 consecutive children screened, DMD was not confirmed genetically in 3, and 20 had an LVEF <55% (mean 45.6 ± 7.0%). Thus, 57 patients were included (28 randomly allocated to group 1, 29 randomly allocated to group 2). There was no difference in baseline characteristics between the two treatment groups (Table 1).

Phase I. Among 56 patients who completed phase I, at least one adverse event was reported by 19 patients in group 1, versus 17 patients in group 2 (Table 2).

LV FUNCTION. At 36 months, LVEF remained normal in the majority of patients, and mean LVEF was similar in both groups. One patient did not complete phase I, though had remained free of cardiovascular event or symptoms at 36 months; LVEF was <45% in a single patient in each group.

Phase II. In phase II, three patients from group 1 and two from group 2 withdrew from the study for personal reasons. None of these five patients experienced an adverse clinical event during that period. Beta-adrenergic blockers were prescribed for treatment of supraventricular arrhythmias in four patients in group 1 and five in group 2. No patient received diuretics or other cardioactive drugs. Mean LVEF decreased from 65.0 ± 5.5% at baseline to 58.6 ± 8.1% at 60 months in group 1 (*p* = 0.001), and from 65.4 ± 5.5% to 56.0 ± 15.5% in group 2 (*p* = 0.006). The difference in mean LVEF between the two groups was not statistically significant. A single patient in group 1 had an LVEF <45% versus eight in group 2, including the patient with an LVEF <45% at the end of phase I (chi-square 5.669, *p* = 0.02) (Fig. 1). The mean age of patients with versus without depressed LVEF was similar, and no difference was observed when comparing the effects of 2 versus 4 mg of perindopril. No patient treated with a beta-adrenergic blocker during phase II had an LVEF <45% at the end of the study. Finally, three patients, who all had an LVEF <45%, died of CHF during an additional year of follow-up in group 2, versus none in group 1 (*p* = 0.08).

Table 1. Baseline Characteristics of Study Groups

| | Group 1 (n = 28) | Group 2 (n = 29) |
|---------------------------------------|---------------------|---------------------|
| Age, yrs | 10.7 ± 1.2 | 10.6 ± 1.2 |
| Weight, kg | 37.1 ± 10.1 | 37.5 ± 13.8 |
| Height, cm | 141 ± 10 | 139 ± 14 |
| Systolic blood pressure, mm Hg | 109 ± 12 | 105 ± 8 |
| Diastolic blood pressure, mm Hg | 64 ± 9 | 61 ± 12 |
| Heart rate, beats/min | 94 ± 12 | 99 ± 15 |
| LVEF, % | 65.0 ± 5.5 | 65.4 ± 5.5 |
| Treatment daily dose of study drug, n | | |
| 2 mg | 9 | 12 |
| 4 mg | 19 | 17 |

Unless specified otherwise, values are means ± SD. Between-group differences are statistically nonsignificant.

LVEF = left ventricular ejection fraction.

DISCUSSION

The main findings of our study were: 1) perindopril administered for 60 months had a preventive effect in children with DMD and normal LVEF between the ages of 9.5 and 13 years; 2) in a dose of 2 to 4 mg/day, perindopril was well tolerated; and 3) LVEF was depressed in 25% of DMD patients before the age of 13 years.

The management of cardiac involvement in DMD is generally supportive and includes ACEI (5). In this study, however, we documented a prophylactic effect of perindopril. This may have important clinical implications, because LV systolic function, unlike ventricular arrhythmias or the standard or signal-averaged electrocardiogram, is a confirmed, powerful prognostic factor in DMD (9). Although our study had been planned for five years, the finding of a trend toward a lower mortality in group 1 at six years of follow-up reinforces our results. Combined with the tolerance of therapy, this suggests that DMD patients should be treated with perindopril as early as 9.5 years of age, regardless of LVEF.

The benefit conferred by perindopril was manifest in the prevention of a decrease in LVEF below 45% at 60 months. No significant difference between the treatment groups was present at the end of the double-blind period, and no difference in mean LVEF was observed at 60 months. The absence of a more prominent treatment effect may have

Table 2. Adverse Events During the Study

| | Group 1 (n = 28) | Group 2 (n = 29) |
|--------------------------|---------------------|---------------------|
| Bronchitis | 2 | 5 |
| Cough | 2 | 3 |
| Rhinitis | 2 | 3 |
| Weight loss | 3 | 2 |
| Fever | 2 | 2 |
| Headache | 2 | 2 |
| Diarrhea | 0 | 2 |
| Minor allergic reactions | 0 | 2 |
| Hyperkalemia | 0 | 0 |
| Renal insufficiency | 0 | 0 |

Values indicate numbers of patients.

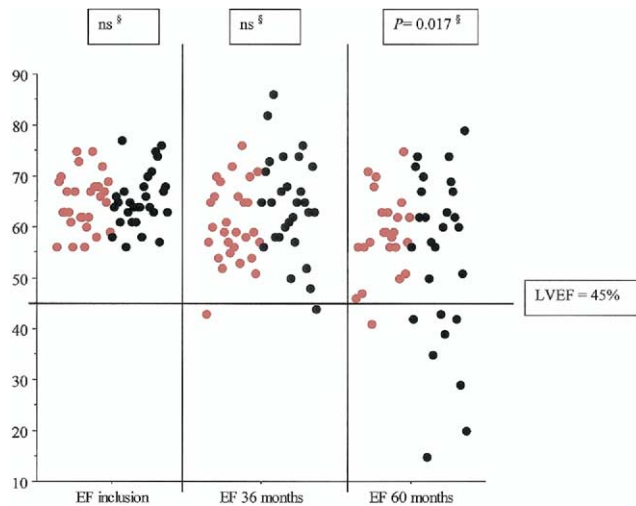


Figure 1. Distribution of left ventricular ejection fraction (LVEF) in groups 1 and 2 at study entry, 36 months, and 60 months of follow-up. §Corresponds to the difference in the number of patients with LVEF <45% in each group. **Red circles** = group 1 (initially assigned to perindopril); **black circles** = group 2 (initially assigned to placebo).

been due to our selection of patients with a preserved baseline LV function, who were, a priori, at lower risk of early cardiac involvement, as confirmed by a preserved LVEF up to 60 months in most patients. The small population studied may also explain the 60-month delay in the development of significant differences between the two study groups. On the other hand, one may wonder why perindopril was apparently ineffective in preventing a decrease in LVEF in group 2 during phase II. In the absence of a control group during phase II, however, one cannot conclude that ACEI perindopril was ineffective. Furthermore, because: 1) cardiac involvement is inescapable in DMD; and 2) our population was older when entering phase II, cardiac involvement may have been present at study entry in some children assigned to placebo, although undetectable by radionuclide ventriculography, and the delayed initiation of ACEI treatment may have failed to prevent further progression of LV dysfunction during phase II (3). This highlights the importance of more sensitive methods of assessment, such as tissue-Doppler echocardiography (10), when planning similar studies.

Our observations also illustrate the variable evolution of

early cardiac involvement in DMD, and the high prevalence of depressed LVEF before 13 years of age. This suggests that studies of preventive treatment with perindopril at a younger age are warranted.

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APPENDIX

For a list of the French investigators and institutions that participated in the study, please see the March 15, 2005, issue of *JACC* at www.onlinejacc.org.