



Perindopril preserves left ventricular function in X-linked Duchenne muscular dystrophy

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KEYWORDS

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Duchenne muscular dystrophy (DMD), an X-linked disorder due to a lack of dystrophin, is associated with muscle weakness and myocardial dysfunction. DMD children between the ages of 9.5 and 13 years with normal left ventricular ejection fraction were included in this prospective study. They were randomly assigned for 3 years to perindopril 2–4 mg (group 1) or placebo (group 2) in a double-blind protocol, followed by open-label treatment with perindopril for all patients. Left ventricular function was compared between the two groups at 5 years. A total of 28 patients were assigned to group 1 and 29 patients were assigned to group 2. Baseline characteristics were similar in both groups. At the end of the 5-year follow-up period, eight patients had an ejection fraction under 45% in the placebo group vs. one patient in the perindopril group ($P < 0.02$). All patients were alive in the perindopril group and three had died in the placebo group ($P = 0.07$). Early initiation of treatment with perindopril is associated with a preservation of left ventricular function in DMD children and with a trend towards a lower mortality.

Introduction

Duchenne muscular dystrophy (DMD; *Figure 1*) is an inherited, X-linked disease characterized by progressive muscle weakness, and it is present in approximately one in 3000 male births.¹ The gene, located at Xp21, codes for dystrophin, a sarcolemmal protein that links the cytoskeleton to the basal lamina via the dystrophin-associated glycoprotein complex.^{2,3} Cardiac involvement is inescapable and, with respiratory failure, is the most common cause of fatal outcome.^{1,4,5} Evidence of myocardial involvement begins with minor electrocardiographic

abnormalities, and evolves towards cardiomyopathy with dilatation of the cardiac chambers and depression of left ventricular (LV) ejection fraction (EF) due to widespread fibrosis; it is responsible for death in approximately 40% of patients aged between 10 and 30 years.^{6–8}

Angiotensin-converting enzyme (ACE) inhibitors have become first-line drugs in the management of patients suffering from congestive heart failure (CHF), since they reduce both morbidity and mortality.^{9,10} On the basis of experimental observation of the salutary effects conferred by perindopril in the Syrian hamster, an animal model of β sarcoglycanopathy that is phenotypically similar to DMD,^{11–13} we examined the preventive merit of the early administration of perindopril in children with DMD and normal LVEF at inclusion, after

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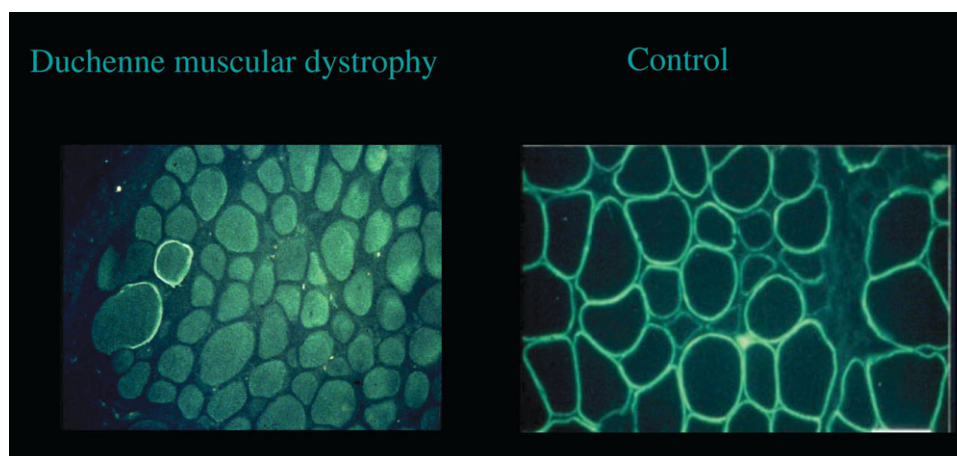


Figure 1 Duchenne muscular dystrophy. Immunohistochemical image of dystrophin in the skeletal muscle. Absence of subsarcolemmal fluorescence in the patient muscle vs. control.

5 years of follow-up. Our results on the prevention of LV dysfunction have recently been published.¹⁴

Patient population and methods

The protocol of this study has previously been described in detail.¹⁴ Briefly, among 80 children screened at 10 medical institutions (Appendix), 57 between the ages of 9.5 and 13 years who had genetically confirmed DMD and a LVEF > 55% measured by radionuclide ventriculography, were included in a two-phase prospective study. Of the remaining patients, 20 had a LVEF that was ≤55%, and three patients did not have confirmed DMD. Additional inclusion criteria included tolerance of a 1-mg test dose of perindopril, and systolic blood pressure that was ≥80 mm Hg in the supine position or >70 mm Hg in the sitting position. Children with contraindications to treatment with an ACE inhibitor, those receiving treatment with other cardioactive drugs, or who had a blood urea nitrogen level of >7 mmol/L, were not included in the study. The protocol was approved by the appropriate Ethics Review Committees, and informed, written consent was obtained from the parents or legal guardians.

Randomization and follow-up

After their inclusion into the study, the children were randomly assigned for 3 years (phase I) in a double-blind fashion to either perindopril 2–4 mg daily as tolerated (group 1, $n = 28$), or to placebo (group 2, $n = 29$). In phase II, all patients were followed during open-label treatment with perindopril, 2–4 mg daily, for two additional years. The main end point was the existence of altered LVEF at 5 years, as assessed by radionuclide ventriculography.¹⁴ Radionuclide ventriculography was not performed in one child at the end of phase I, and in six children at the end of phase II.

The prescription of other cardioactive drugs was allowed during phase II at the discretion of the primary care physicians.

Statistical analysis

Data expressed as mean ± standard deviation were analysed according to the intention-to-treat principle, and LVEF measurements that were available were included in the analysis at each time point. Student's t -tests were used for normally distributed continuous variables, and χ^2 -analysis for differences in frequencies. All P -values were two-tailed and a P -value of <0.05 was considered statistically significant (Statview software, Abacus concept, Berkeley, Ca).

Results

The baseline characteristics of the study groups were similar (*Table 1*). No pharmaceutical agent other than the study drugs was administered during phase I. During phase II, treatment with perindopril was continued in the maximum tolerated doses in all patients. In addition, at the beginning of phase II, four patients in group 1 (initially allocated to perindopril) and five in group 2 (initially allocated to placebo) were treated with β -adrenergic blockers. All patients were still receiving treatment with perindopril at the end of phase II. None of the patients were treated with digoxin, spironolactone, or steroids during any part of the study; none had implantable devices, including cardioverter defibrillators or cardiac pacemakers. Compliance to prescription was fair in all children.

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 events or symptoms at 36 months; LVEF was <45% in a single patient in each group.

Table 1 Baseline characteristics of the two study groups described

| | Perindopril, group 1 (n = 28) | Placebo, group 2 (n = 29) |
|--|-------------------------------|---------------------------|
| Age (years) | 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 (b.p.m.) | 94 ± 12 | 99 ± 15 |
| Left ventricular ejection fraction (%) | 65.0 ± 5.5 | 65.4 ± 5.5 |
| Daily dose of the assigned study drug (phase I period): 2/4 mg (n) | 9/19 | 12/17 |

Unless otherwise specified, values given are the mean ± SD.

After 5 years' follow-up, perindopril delayed the onset and progression of LV dysfunction; in the actively-treated group, only a single patient had a LVEF <45%, vs. eight patients in the group assigned to placebo ($P = 0.02$).¹⁴ None of the patients died in the perindopril group, compared with three patients in the placebo group ($P = 0.07$).

Discussion

We have previously reported that during the 5-year follow-up period of our study, perindopril delayed the onset and progression of LV dysfunction: in the actively-treated group, a single patient had an LVEF <45% at 5 years, compared with eight patients in the group assigned to placebo ($P = 0.02$).¹⁴ We documented a benefit on LVEF conferred by the early, instead of delayed, administration of perindopril in DMD children between the ages of 9.5 and 13 years presenting with normal LVEF at entry into the study. While several other studies have reported a lowering of mortality with ACE inhibitors in patients suffering from congestive heart failure¹⁰ or a preventive effect in patients at high risk of adverse cardiovascular events,¹⁵ ours is the first to demonstrate a benefit conferred by perindopril on LVEF in patients with normal ejection fraction at inclusion and lacking dystrophin, an orphan disease genetically determined to develop LV dysfunction.

In addition to a preservation of LVEF, we also report a trend towards a lower mortality in the perindopril group; this result is in accordance with the recent Candesartan in Heart Failure Reduction in Mortality (CHARM) study conducted in the adult population with heart failure, which used the same cut-off of 45% for LVEF and demonstrated that patients with an LVEF <45% had an increased mortality during follow-up.¹⁶

Table 2 Mechanisms of angiotensin-converting enzyme inhibition in the prevention of left ventricular dysfunction in Duchenne muscular dystrophy

| |
|---|
| Renin-angiotensin-aldosterone system inhibition |
| Decrease in angiotensin II |
| Blockade of the degradation of bradykinin |
| Reduction in aldosterone |
| Afterload reduction |
| Prevention of myocyte necrosis and apoptosis |
| Maintaining myocyte regeneration capacities |
| Limitation of myocardial fibrosis |
| Improvement in diaphragmatic contractility |
| Restoration of neutral nitric oxide synthase activity in the dystrophin-associated glycoprotein complex |

The gradual onset of the treatment effect and the progressive benefit over time that we observed are consistent with an haemodynamic effect and/or a specific antifibrotic effect of perindopril, and are concordant with experimental observations made in a model of progressive cardiomyopathy resembling Duchenne myopathy.^{12,13}

Dystrophin in fact plays a critical role in the myocardium by connecting the cytoskeleton to the external basement membrane. Its absence is responsible for membrane fragility, loss of transductional force and, ultimately, myocyte necrosis promoted by mechanical stress.^{17,18} Thus, afterload reduction by perindopril may be a key factor in our study, which included children with DMD who were, on an average, less than 11 years of age.¹⁹ Some of the children were still capable of muscular exercise, and there is experimental evidence that the myocardium is vulnerable to pressure overload.²⁰ The inhibition of aldosterone synthesis by ACE inhibitors might also prevent the development of fibrosis,^{21,22} and previous studies have demonstrated a beneficial effect of such inhibition.^{23,24} Finally, nitric oxide (NO), a powerful antioxidant, might also be involved in the development of cardiac dysfunction in DMD. Mutation of dystrophin is accompanied by loss of dystrophin-associated glycoprotein complex, which includes neural NO synthase.²⁵ The restoration of neural NO synthase activity in an animal model was found to result in NO synthesis and limitation of myocardial fibrosis without an increase in the expression of membrane-associated cytoskeletal proteins.^{26,27} Since ACE inhibitors stimulate the synthesis of NO first by blocking the degradation of bradykinin by the direct promotion of the bradykinin type 2 receptor coupling to NO storage sites²⁸ and second by inhibiting aldosterone,²⁹ they may exert part of their beneficial effects via a NO-related pathway (*Table 2*).

Beyond cardiac involvement, DMD is also characterized by a progressive deficit of intercostal muscles and diaphragmatic function, leading to severe chronic respiratory insufficiency. Furthermore, previous experimental studies have observed a beneficial effect of ACE inhibition on diaphragmatic contractility.³⁰ More recently, using the Mdx mouse – an animal model lacking dystrophin – it has been demonstrated that blocking the renin angiotensin pathway very early before the beginning of the fibrosis

process preserves the muscle function of these mice by maintaining stem cell myoblast regeneration.³¹ Although the beneficial effects that we observed on heart function may not be attributed to myocyte regeneration capacity, our overall results suggest a global favourable effect on both heart and skeletal muscle.^{14,31}

Clinical implications

Our study may have important implications in the management of patients with DMD. We and others had reported the preventive effect of ACE inhibition against LV contractility deterioration.^{14,32,33} However, there is still ongoing controversy as to whether DMD patients should be treated early (preventively) with ACE inhibitors.^{34–36} Since we limited the study entry to patients between the ages of 9.5 and 13 years, the optimal age for initiation of therapy remains to be determined.¹⁴ The recent documentation of reduced myocardial strain by magnetic resonance imaging in 13 children with DMD whose mean age was the same as that of our patients,³⁷ supports the earlier introduction of ACE inhibitor treatment, a hypothesis that warrants further scrutiny.

Study limitations

The randomized, double-blind phase of our protocol was limited to 3 years, after which perindopril was dispensed in an open-label fashion. Although this could be highly criticized, our approach might be considered as valid in this particular setting of a rare disease. Moreover, the inclusion of all patients throughout a prolonged follow-up period and the continuation of perindopril in all patients during the open-label period, associated with adequate compliance, were strengths of the study.

Although this study is one of the largest studies of DMD, it was not powered to analyse mortality, and the trend towards lower mortality must be interpreted with caution.

Only a few patients were treated with β -adrenergic blockers, as this study had been planned before the demonstration and wide acceptance of their efficacy in the management of heart failure. In addition, respiratory insufficiency, often present in these patients, may be viewed as a contraindication to β -blockade, although we do not share this opinion.

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Conflict of interest: none declared.

Appendix

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