Treatment of dilated cardiomyopathy with carvedilol in children

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SUMMARY: Erdoğan İ, Özer S, Karagöz T, Çeliker A, Özkutlu S, Alehan D. Treatment of dilated cardiomyopathy with carvedilol in children. Turk J Pediatr 2009; 51: 354-360.

We performed a study to examine the clinical use of carvedilol, its dosage and its effects on systolic functions in children. Twenty-one patients with dilated cardiomyopathy who were treated with carvedilol adjacent to standard heart failure therapy were enrolled in the study. Echocardiographic assessment was obtained before and during carvedilol therapy, and left ventricular fractional shortening and left ventricular ejection fraction were determined in order to estimate left ventricular function. At a follow-up of six months, left ventricular ejection fraction and fractional shortening significantly improved from 38±10% to 53±13% and from 19±6 % to 27±8%, respectively, following carvedilol treatment. The results of the present study indicate that carvedilol is well tolerated in children with dilated cardiomyopathy and there is a significant improvement in the clinical status and left ventricular ejection fraction in patients not responding to conventional therapy. Patient selection criteria, optimal timing of carvedilol therapy, its dosage and its long-term effects need to be investigated with multi-institutional trials and large numbers of patients.

Key words: carvedilol, heart failure, beta-blocker, dilated cardiomyopathy, treatment.

Beta-blockers have been shown to have a favorable effect in the treatment of congestive heart failure in adult patients[1,2]. Randomized clinical trials in heart failure have shown that treatment improves symptoms by increasing cardiac systolic functions and remodeling the dilated ventricles[1,3]. Carvedilol has been shown to improve survival, decrease morbidity and improve quality of life in adults with congestive heart failure[2,7]. Carvedilol, a nonselective beta-blocker, decreases the chronic adrenergic overstimulation of the myocardium and improves myocardial function[1]. Additionally, by its α_1–receptor blockade effect, it acts as a systemic arterial vasodilator[8,9]. While carvedilol reduces the morbidity and mortality of congestive heart failure in adult patients, little is known about its effects and appropriate dosing among children with congestive heart failure[1,3]. The aim of this study was to examine the clinical use of carvedilol, its dosage and its effects on systolic functions among children.

Material and Methods

This study was performed on 21 children (10 male, 11 female) with congestive heart failure with dilated cardiomyopathy admitted to our center between 2000 and 2006. The local ethics committee gave approval for the study. The mean age of patients was 64±55 months (range: 5 months-16 years). Diagnoses were: idiopathic dilated cardiomyopathy (n: 17), anthracycline- induced cardiomyopathy (n: 2), dilated cardiomyopathy after atrial septal defect repair (n: 1), and Duchenne muscular dystrophy (n: 1).

All patients received digoxin, diuretics, angiotensin-converting enzyme inhibitor, and coenzyme Q-10 for at least three months before starting carvedilol therapy.

The patients received an initial dose of 0.05 mg/kg/day (maximum 3.125 mg/day) of carvedilol in two doses. Carvedilol dose was increased weekly to achieve 0.5 mg/kg/day (maximum 25-50 mg/day) in two doses in 8-10 weeks.

Heart rate and blood pressure were monitored at least 24 hours at the beginning of the treatment and for four hours at each dose increment.

Heart failure symptoms were reviewed before and during carvedilol treatment according to clinical score modified from Ross[10] and Reithmann et al.[3] (Table I). Electrocardiography and Holter monitoring were performed before and during carvedilol treatment.

Echocardiographic assessment was obtained before and during carvedilol therapy, and left ventricular fractional shortening and left ventricular ejection fraction were determined in order to estimate left ventricular function.

Statistical analysis

Data are expressed as mean±standard deviation, range or percentage. Comparison between echocardiographic parameters and clinical differences before and after carvedilol treatment was made using the Student's t-test. Differences were considered significant for p values less than 0.05.

Results

Before and after carvedilol

Clinical status and side effects (Table II)

After six months of treatment with carvedilol, the clinical score significantly improved from 5.3 points to 1.1 points ($p<0.05$). In 1 patient (5 months old), heart failure had worsened severely in the third week of uptitration of carvedilol, and we discontinued the treatment. Carvedilol was discontinued because of hypotension in another patient (15 years old) in the third month of treatment. No untoward events occurred in the other patients. One patient with anthracycline–induced cardiomyopathy died because of neutropenic sepsis after six months of follow-up with carvedilol treatment.

Arrhythmias (Table II)

Electrocardiography interpretation and Holter monitoring were performed in all patients before and after carvedilol. Before treatment, 7 patients (33%) had ventricular ectopic beats; however, they disappeared in 6 patients and in 1 patient decreased with carvedilol; 14 patients had normal sinus rhythm. We did not observe ventricular tachycardia in any patient.

Digoxin level

Serum digoxin levels were measured in all patients before the treatment and after uptitration of carvedilol. None of the patients had values above therapeutic levels.

Brain natriuretic peptide (Table II)

We assessed brain natriuretic peptide levels in 8 patients before and six months after carvedilol treatment. The brain natriuretic peptide levels

Table I. Clinical Score Modified from Ross[10] and Reithmann et al.[3, 4]

Score Points	0	1	2
History			
Diaphoresis	Head only	Head and body during exercise	Head and body at rest
Tachypnea	Rare	Several times	Frequent
Physical examination			
Breathing	Normal	Retractions	Dyspnea
Respiratory rate (respirations/min)			
0-1 y	<50	50-60	>60
1-6 y	<35	35-45	>45
7-10 y	<25	25-35	>35
11-14 y	<18	18-28	>28
Heart rate (beats/min)			
0-1 y	<160	160-170	>170
1-6 y	<105	105-115	>115
7-10 y	<90	90-100	>100
11-14 y	<80	80-90	>90
Hepatomegaly (liver edge from right costal margin)	<2 cm	2-3 cm	>3 cm

Table II. Clinical Parameters and Brain Natriuretic Peptide Levels of Patients

	Before carvedilol	After carvedilol	P
Clinical score (Ross) (points) (n: 19)	5.3	1.1	<0.05
BNP (pg/ml) (n: 8)	420±260	225±131	<0.05
Arrhythmias (HOLTER: VEB) (n: 19)	7	1	<0.05

BNP: Brain natriuretic peptide. VEB: Ventricular ectopic beats.

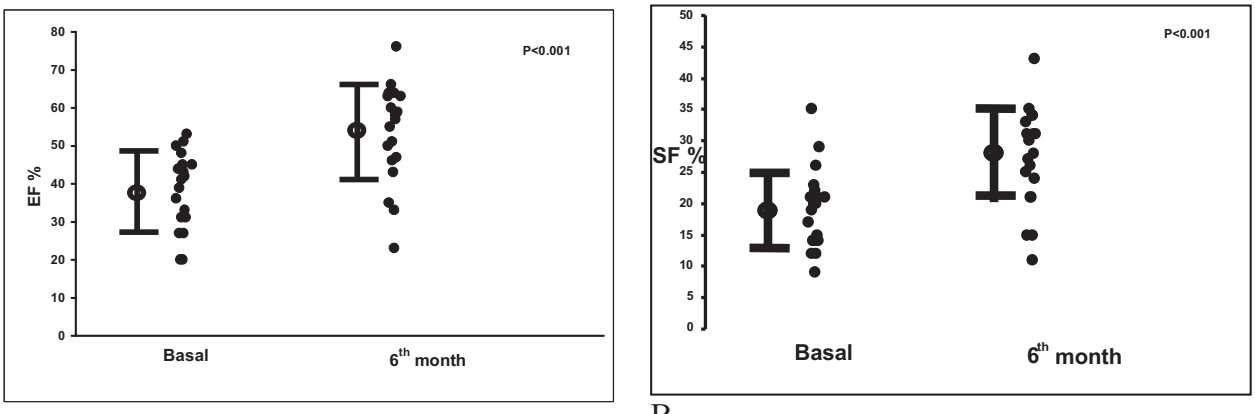
significantly decreased after starting carvedilol (420±260 pg/ml, 225±131 pg/ml, respectively; p<0.05).

Left ventricular function on echocardiography (Tables III, IV)

Left ventricular ejection fraction significantly improved, from 38±10% (range: 20–53%) to 53±13% (range: 23–76%), following carvedilol treatment (p<0.001) (Fig. 1). A significant increase in left ventricular ejection fraction was not observed in 3 patients with idiopathic dilated cardiomyopathy; however, these 3 patients had significant clinical benefit so the therapy was continued. The left ventricular fractional shortening increased from 19±6% (range: 9–35%) to 27±8% (range: 11–43%) after six months with carvedilol treatment (p<0.001) (Fig. 1). The left ventricle end-diastolic dimensions significantly decreased from 47±8 mm (range: 31–60 mm) to 43±10 mm (range: 26–63 mm) with carvedilol treatment (p<0.05). The left ventricle end-systolic dimensions significantly decreased, from 36±7 mm (range: 24–52 mm) to 31±9 mm (range: 15–53 mm) with carvedilol treatment (p<0.05).

Discussion

Carvedilol, a nonselective beta-blocker, decreases the chronic adrenergic overstimulation of the myocardium and improves myocardial function[1,2]. Additionally, by its α_1–receptor blockade effect, it acts as a systemic arterial vasodilator[11]. The mechanisms of action of carvedilol in congestive heart failure include reversal of adrenergic-induced ventricular remodeling, improvement in intrinsic ventricular function, vasodilatation, decreased stimulation of neurohumoral systems, and antioxidant effects. The beta-blockers have been shown to have a favorable effect in the treatment of congestive heart failure and reduce the morbidity and mortality of congestive heart failure in adult patients, but little is known about the effects and appropriate dosing among children with congestive heart failure[1,4]. Carvedilol may have similar mechanisms of action in children as that of beta-blockers in adult patients. Recent studies have shown that beta-blocker therapy decreases the risk of hospitalization and death in dilated cardiomyopathy patients. The clinical beneficial effect of carvedilol is suggested by the modified Ross clinical score. Laer et al.[12] reported improvement of the clinical score



A B

Fig. 1. Change in ejection fraction and shortening fraction from baseline to 6 months of carvedilol treatment. (A) Ejection fraction at entry and at 6 months of carvedilol treatment. There was a significant change in ejection fraction in 6 months (p<0.001). (B) Shortening fraction at entry and at 6 months of carvedilol treatment. There was a significant change in shortening fraction in 6 months (p<0.001) (EF: Ejection fraction. SF: Shortening fraction).

Table III. Clinical and Hemodynamic Parameters of Patients

Patient no.	Age (months)	Gender	DCM	Before carvedilol				After carvedilol				Side effects
				LVESD (mm)	LVEDD (mm)	LVEF (%)	LVSF (%)	LVESD (mm)	LVEDD (mm)	LVEF (%)	LVSF (%)	
1	15	F	idiopathic	37	42	27	12	44	48	23	11	–
2	108	M	AICMP	46	54	31	14	31.2	45.5	59	31	–
3	192	M	AICMP	33	51	42	21	33	51	63	34	–
4	12	F	idiopathic	34	43	44	21	21	33	64	31	–
5	36	F	idiopathic	29	38	48	23	22	31	55	27	–
6	15	F	idiopathic	28	57	20	14	21	33	66	35	–
7	84	F	idiopathic	52	60	27	12	53	63	33	15	–
8	30	M	idiopathic	32	35	20	9	24	33	57	28	–
9	18	F	idiopathic	24	31	43	20	24	31	46	21	–
10	36	M	idiopathic	42	51	36	17	39	50	43	21	–
11	72	F	idiopathic	46	55	31	14	35	50	35	15	–
12	120	F	ASD	34	51	45	21	30	50	60	30	–
13	60	M	idiopathic	26	36	50	35	25	36	64	34	–
14	168	M	DMD	37	52	53	29	40	53	58	31	–
15	24	M	idiopathic	40	50	41	20	40	52	47	24	–
16	5	M	idiopathic	31	37	33	15	15	26	76	43	–
17	15	M	idiopathic	35	49.4	51	26	36	48	50	25	–
18	96	M	idiopathic	43	53	39	19	25	38	63	33	–
19	108	F	idiopathic	33	43	45	22	33	45	51	26	–
20	180	F	idiopathic	32	42	45	21	–	–	–	–	Hypo–tension
21	5	F	idiopathic	38	44	30	13	–	–	–	–	CHF ↑

AICMP: Anthracycline-induced cardiomyopathy. ASD: Atrial septal defect. CHF: Congestive heart failure. DCM: Dilated cardiomyopathy. DMD: Duchenne muscular dystrophy. LVEDD: Left ventricle end diastolic dimension. LVEF: Left ventricle ejection fraction. LVESD: Left ventricle end systolic dimension. LVSF: Left ventricle shortening fraction.

Table IV. Echocardiographic Parameters of Patients

	Before carvedilol		After carvedilol		
	Mean±SD	Range	Mean±SD	**Range**	P
LVESD (mm)	36±7	24-52	31±10	15-53	<0.001
LVEDD (mm)	47±8	31-60	43±10	26-63	<0.001
LVSF (%)	19±6	9-35	27±8	11-43	<0.001
LVEF (%)	38±10	20-53	53±13	23-76	<0.001

SD: Standard deviation. LVESD: Left ventricle end systolic dimension. LVEDD: Left ventricle end diastolic dimension. LVSF: Left ventricle shortening fraction. LVEF: Left ventricle ejection fraction.

from 5 to 3 points in six months of treatment in children. In our study, the clinical score had significantly improved from 5.3 to 1.1 points and except for during the uptitration period, none of the patients had required hospitalization in the six-month follow-up. Symptomatic improvements of patients and similarity of the results of studies to adult trials show that carvedilol is efficacious in the management of dilated cardiomyopathy in children.

Despite the symptomatic improvement with carvedilol therapy, adverse events were also reported[1,2]. The adverse event ratio was found to be 30% in the study of Bruns et al.[1], and 10 different side effects (hypoglycemia, bradycardia, diaphoresis, worsening of heart failure, atrial fibrillation, low cardiac output, heartburn symptoms, viral gastroenteritis, upper respiratory infection, hypertonic neurological symptoms) had been observed in the study of Blume et al.[2] In the study of Bruns et al.[1], 3 of 46 patients and in the study of Blume et al.[2] 1 of 12 patients withdrew during uptitration because of worsening of heart failure. In our study, the side effects were very limited and we discontinued carvedilol in one patient (5 months old) because of worsening of heart failure in the third week of uptitration and in another one (15 years old) because of hypotension in the third month of treatment. The low incidence of adverse events in the present study may be attributed to our starting carvedilol in small doses and gradually increasing the dose over a period of several weeks to provide safety of the drug. All patients were hospitalized during initiation and uptitration of carvedilol. The dose of carvedilol was less than that of these two studies (0.08 mg/kg/day and 0.1 mg/kg/day, respectively). Our results demonstrate that carvedilol was well tolerated by children even in small infants. It should be emphasized that carvedilol therapy should be initiated in small doses and gradually increased over a period of several weeks to ensure the safety of the patient. Carvedilol seems to be benign, even if there are some observed and reported side effects. However, all patients should be monitored for side effects of the drug.

Some investigators suggest that carvedilol may have an additional beneficial effect on the reduction of arrhythmias, especially in adult patients[11]. To our knowledge, studies about the effect of carvedilol on arrhythmias in dilated cardiomyopathy in pediatric patients are very limited in the literature. In the present study, Holter monitoring was performed in all of the patients before and after carvedilol. We observed that ventricular ectopic beats disappeared in six patients and decreased in one patient with carvedilol treatment, and Holter monitoring was normal in 14 patients who were treated with carvedilol for six months both before and after the treatment. These findings suggest that carvedilol is also effective in the control of ventricular ectopic beats in pediatric patients.

Digoxin concentrations increase when digoxin and carvedilol are administered concomitantly[13]. The findings of the study of Aiba et al.[13] indicate that the intestinal absorption of digoxin is primarily dominated by the efflux process on the luminal side of the intestine, and that carvedilol may vary the rate of intestinal digoxin absorption mainly by inhibiting this efflux process. The study of Ratnapalan et al.[14] showed that carvedilol increases serum concentrations of digoxin in children, and its dose may need to be reduced to avoid toxicity. Digoxin level was determined in all patients and it was seen that digoxin was in therapeutic levels in our study. Digoxin dose was decreased to the lower limit of the recommended dose based on body weight when we started carvedilol. Thus, it is important to determine serum digoxin level in specific periods to decide on any reduction while the patients receive carvedilol therapy.

Neurohumoral markers have been associated with prognosis of congestive heart failure. Brain natriuretic peptide is the most widely used marker for the follow-up and a rapid point-of-care assay. Recent studies reported that carvedilol therapy is associated with a sustained decline in brain natriuretic peptide levels[15,17]. We assessed brain natriuretic peptide levels in eight patients before and six months after carvedilol treatment. The brain natriuretic peptide levels significantly decreased after starting carvedilol. Serial brain natriuretic peptide levels can provide some guidance regarding probability of left ventricular ejection fraction improvement.

Carvedilol blocks the deleterious effects of chronic adrenergic overstimulation of the myocardium and improves myocardial function[18]. Several studies have demonstrated a favorable effect of carvedilol on left ventricle dimensions, shape and left ventricular systolic function[11]. Left ventricular ejection fraction improved from 32% to 41% between 1 month and 19 months in 45 patients in the study of Laer et al.[12]; from 36% to 54% in 6 months in 15 patients in the study of Bruns et al.[1]; and from 24.6% to 42.2% in 6 months in the study of Rusconi et al.[19] In the present study, the left ventricular ejection fraction significantly improved, from 38% to 53%, after 6 months of carvedilol treatment. In three patients, a significant increase in left ventricular ejection fraction was not observed, but these three patients had significant clinical benefit, so the therapy was continued. Left ventricular fractional shortening improved from 18% to 26% in 6 months in 15 patients in the study of Laer et al.[12]; from 16% to 19% in 6 months in the study of Bruns et al.[1]; and from 19% to 27% after 6 months in our study ($p<0.001$).

Carvedilol with its antioxidant effect may limit the extent of cardiomyopathy associated with cumulative doxorubicin therapy[20]. The study of Santos et al.[20] showed that carvedilol protects against both the structural and functional cardiac tissue damage. In our study, we started carvedilol in two patients with anthracycline-induced cardiomyopathy after three months of standard heart failure therapy. In both, left ventricular ejection fraction had increased significantly and clinical status improved after carvedilol therapy. This result is very important. The patients who receive anthracycline should be followed closely; administration of carvedilol may prevent further cardiac damage whenever cardiac insufficiency is determined.

There were no deaths except for the neutropenic patient with malignancy in this group of patients during the study period. However, the total number of patients was small and the follow-up period was not long enough to determine the impact of carvedilol on the survival of children with dilated cardiomyopathy.

In conclusion, the results of the present study indicate that carvedilol is well tolerated in children with dilated cardiomyopathy, and there was significant improvement in the functional status and left ventricular ejection fraction in patients not responding to conventional therapy, even in small infants. The dose of carvedilol in the present study seems to be safe and efficient. Although the optimal treatment for dilated cardiomyopathy in children is not known, the addition of carvedilol to the standard therapy may improve the symptoms of congestive heart failure, ventricular function and survival. When the patients' clinical and laboratory findings were examined before and after carvedilol treatment, decrease in modified Ross score, decrease in brain natriuretic peptide level, increase in left ventricular ejection fraction and left ventricular fractional shortening, and decrease in left ventricle end-systolic dimensions and left ventricle end-diastolic dimensions were observed. Our data have revealed that carvedilol treatment improved heart failure and arrhythmia and led to a better quality of life. The number of children in our study was limited and further studies are needed in a large number of patients. On the other hand, to understand if the drug extends survival, it would be very useful to compare patients receiving treatment with those who do not over an extended period of time.

REFERENCES

1. Bruns LA, Chrisant MK, Lamour JM, et al. Carvedilol as therapy in pediatric heart failure: an initial multicenter experience. J Pediatr 2001; 138: 505-511.
2. Blume ED, Canter CE, Spicer R, Gauvreau K, Colan S, Jenkins KJ. Prospective single-arm protocol of carvedilol in children with ventricular dysfunction. Pediatr Cardiol 2006; 27: 336-342.
3. Reithmann C, Reber D, Kozlik-Feldmann R. A post-receptor defect of adenylyl cyclase in severely failing myocardium from children with congenital heart disease. Eur J Pharmacol 1997; 330: 79-86.
4. Läer S, Mir TS, Behn F, et al. Carvedilol therapy in pediatric patients with congestive heart failure: a study investigating clinical and pharmacokinetic parameters. Am Heart J 2002; 143: 916-922.

5. Tatli E, Kurum T. A controlled study of the effects of carvedilol on clinical events, left ventricular function and proinflammatory cytokines levels in patients with dilated cardiomyopathy. Can J Cardiol 2005; 21: 344-348.
6. Packer M, Bristow MR, Cohn JN, et al. The effect of carvedilol on morbidity and mortality in patients with chronic heart failure. U.S. Carvedilol Heart Failure Study Group. N Engl J Med 1996; 334: 1349-1355.
7. Colucci WS, Packer M, Bristow MR, et al. Carvedilol inhibits clinical progression in patients with mild symptoms of heart failure. Circulation 1996; 94: 2800-2806.
8. Shaddy RE, Tani LY, Gidding SS, et al. Beta-blocker treatment of dilated cardiomyopathy with congestive heart failure in children: a multi-institutional experience. J Heart Lung Transplant 1999; 18: 269-274.
9. Spicer RL. Carvedilol - a new dimension in pediatric heart failure therapy. J Pediatr 2001; 138: 457-458.
10. Ross RD. Grading the severity of congestive heart failure in infants. Pediatr Cardiol 1992; 13: 72-75.
11. Gachara N, Prabhakaran S, Srinivas S, Farzana F, Krishnan U, Shah MJ. Efficacy and safety of carvedilol in infants with dilated cardiomyopathy: a preliminary report. Indian Heart J 2001; 53: 74-78.
12. Laer S, Mir TS, Behn F, et al. Carvedilol therapy in pediatric patients with congestive heart failure: a study investigating clinical and pharmacokinetic parameters. Am Heart J 2002; 143: 916-922.
13. Aiba T, Ishida K, Yoshinaga M, Okuno M, Hashimoto Y. Pharmacokinetic characterization of transcellular transport and drug interaction of digoxin in Caco-2 cell monolayers. Biol Pharm Bull 2005; 28: 114-119.
14. Ratnapalan S, Griffiths K, Costei AM, Benson L, Koren G. Digoxin-carvedilol interactions in children. J Pediatr 2003; 142: 572-574.
15. Frantz RP, Olson LJ, Grill D, et al. Carvedilol therapy is associated with a sustained decline in brain natriuretic peptide levels in patients with congestive heart failure. Am Heart J 2005; 149: 541-547.
16. Stanek B, Frey B, Hulsmann M, et al. Prognostic evaluation of neurohumoral plasma levels before and during beta-blocker therapy in advanced left ventricular dysfunction. J Am Coll Cardiol 2001; 38: 436-442.
17. Takeda Y, Fukutomi T, Suzuki S, et al. Effects of carvedilol on plasma B-type natriuretic peptide concentration and symptoms in patients with heart failure and preserved ejection fraction. Am J Cardiol 2004; 94: 448-453.
18. Azeka E, Franchini Ramires JA, Valler C, Alcides Bocchi E. Delisting of infants and children from the heart transplantation waiting list after carvedilol treatment. J Am Coll Cardiol 2002; 40: 2034-2038.
19. Rusconi P, Gomez-Marin O, Rossique-Gonzalez M, et al. Carvedilol in children with cardiomyopathy: 3-year experience at a single institution. J Heart Lung Transplant 2004; 23: 832-838.
20. Santos DL, Moreno AJ, Leino RL, Froberg MK, Wallace KB. Carvedilol protects against doxorubicin-induced mitochondrial cardiomyopathy. Toxicol Appl Pharmacol 2002; 185: 218-227.