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Carvedilol therapy in pediatric patients with dilated cardiomyopathy

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Carvedilol reduces mortality and hospitalization in adults with congestive heart failure. Limited information is available about its use in children. The objective of this study was to determine the dosing, efficacy and side effects of carvedilol for the management of dilated cardiomyopathy in children.

Sixteen children with idiopathic dilated cardiomyopathy, aged 7 months to 138 months and with an ejection fraction less than 40%, were treated with carvedilol. The average initial dose was 0.1 mg/kg/day and it was uptitrated to 0.4 mg/kg/day. After six months on carvedilol, there were improvements in clinical scoring system from an average of 2.94 to 2.50 ($p<0.05$), in mean fractional shortening from 17.2±6.1% to 22.7±5.1% ($p<0.05$), and in ejection fraction from 35.2±6.8% to 43.1±11.2% ($p<0.05$). No side effect was observed during the study period. Two patients died due to serious infection.

Carvedilol in addition to standard therapy for dilated cardiomyopathy in children improves cardiac function and symptoms. It is well tolerated, with minimal adverse effects, but close monitoring is necessary.

Key words: carvedilol, children, dilated cardiomyopathy.

Beta-blocking agents have been shown to have a favorable effect in the treatment of adult patients with heart failure in several randomized, controlled trials[1]. Prospective trials in adults have shown a decreased risk of death and hospitalization, improved ejection fraction and New York Heart Association functional class, and reduced clinical progression in patients with mild heart failure[2-4]. However, as for most pharmacologic agents, little prospective information exists about the use of carvedilol in children with ventricular dysfunction from dilated cardiomyopathy. The purpose of this study was to report our experience using carvedilol in managing children with dilated cardiomyopathy, and to evaluate its dosing, safety, and efficacy.

Material and Methods

The study group included 16 patients diagnosed as idiopathic dilated cardiomyopathy between 2005 and 2006, and who, despite optimization of standard treatment with digoxin, angiotensin converting enzyme inhibitors, and diuretics for at least four months had persistent left ventricular ejection fraction ≤40%. Once patients were identified and informed consent was obtained, in addition to collection of comprehensive baseline demographic and clinical information, all patients underwent echocardiographic evaluation to estimate left ventricular function and to measure fractional shortening before initiation of carvedilol. Patients took a first dose of 0.1 mg/kg carvedilol followed by hourly assessments of blood pressure and heart rate. If the patients tolerated the first dose, while continuing usual baseline medications, all patients began carvedilol at an oral dose of 0.1 mg/kg/day divided twice daily. This dose was uptitrated every two weeks (the dosage was doubled) as tolerated to a target level of 0.4 mg/kg/day, and it was maintained for at least an additional six months. During this time, patients were on standard therapy with all other heart failure medications. Adjustment in the standard medical therapy was at the discretion of the physician.

The primary study end point was change in left ventricular function, estimated as echocardiographic ejection fraction and fractional

shortening. One experienced pediatric cardiologist performed echocardiography (HP Sonos 5500). The follow-up symptom scores and echocardiographic assessments were obtained serially throughout each patient's course.

A modified scoring system of congestive heart failure signs and symptoms described by Ross[5] and Reithmann et al.[6] (Table I) was used for clinical assessments of the patients according to the Laer et al.[7] classification.

Changes in left ventricular ejection fraction and fractional shortening, left ventricular end diastolic and systolic diameters and clinical symptom scores before and after six months of treatment were compared with use of the Wilcoxon signed rank test for matched pairs. A p value <0.05 was considered to be significant. SPSS statistics program was used for statistical analysis of the data.

Results

Sixteen children (8 female, 8 male; age range: 7 months to 138 months) were enrolled in the study. Initial characteristics of the study population are shown in Table II. Mean age of the patients at the beginning of the study was 60.8±35.7 months, and mean age of the patients at the time of diagnosis of

Table I. Clinical Score Modified from Ross[5] and Reithmann et al.[6]

	Score (points)		
History	0	1	2
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 (respiration/min)			
0-1 year	<50	50-60	>60
1-6 years	<35	35-45	>45
7-10 years	<25	25-35	>35
11-14 years	<18	18-28	>28
Heart rate (beats/min)			
0-1 year	<160	160-170	>170
1-6 years	<105	105-115	>115
7-10 years	<90	90-100	>100
11-14 years	<80	80-90	>90
Hepatomegaly (liver edge from right costal margin)	<2 cm	2-3 cm	>3 cm

From Laer et al.[7].

Table II. Initial Characteristics of Patients in the Study (n=16)

Age at the time of diagnosis of cardiomyopathy mean (minimum-maximum, median)	27±30 months (3-108, 14)
Age at entry mean (minimum-maximum, median)	60.8±35.7 months (7-138, 63)
Gender	8 female/8 male
Morphologic left systemic ventricle	16
Mean left ventricular ejection fraction mean (minimum-maximum, median)	35.2±10.7% (16-45.9, 35.5)
Mean left ventricular fractional shortening mean (minimum-maximum, median)	17.2±6.1% (8-24.6, 18)
Concomitant medications	
Digoxin	16
Diuretics	15
ACE inhibitor	15

ACE: Angiotensin converting enzyme.

dilated cardiomyopathy was 27±30 months. As standard treatment, 16/16 (100%) were on digoxin, 15/16 (93.8%) on furosemide, 15/16 (93.8%) on angiotensin converting enzyme inhibitor, and 14/16 (87.5%) on aspirin. The initial mean dose of carvedilol for all treated patients was 0.13±0.06 mg/kg/day, and all patients were uptitrated to 0.45±0.15 mg/kg/day. Mean follow-up of the patients treated with carvedilol was 12±5.8 months. All patients tolerated the highest dose of carvedilol, and 14 of the 16 patients completed the planned six-month course of carvedilol therapy. The remaining two patients died during the study period due to serious infection. One of them was five months old when the study started. Fractional shortening and ejection fraction of this patient were found to be 12% and 28%, respectively, before carvedilol, and 11% and 17%, respectively, at the time of death, which occurred three months after the carvedilol treatment was started. The other, who was 33 months old when the study started, had fractional shortening and ejection fraction of 10% and 21%, respectively, at entry and, 21% and 45%, respectively, at the time of death, which occurred five months later.

Overall, improvements were observed after six months of carvedilol therapy in ejection fraction (35.2±10.7 % vs 43.1±11.2%; p<0.05) and fractional shortening (17.2±6.1% vs 22.7±5.1%; p<0.05) (Table III and Fig. 1). Carvedilol was associated with a decrease in arterial pressure (92.5±13.9/59.3±10.6 mmHg vs 87.5±7.5/59.3±4.4 mmHg; p>0.05) and heart rate (123.8±30.6 beats/min vs 98.8±21.1 beats/min; p<0.05). After six months of treatment with carvedilol, the clinical score improved from an average of 2.94 to an average of 2.50 (p<0.05).

No serious adverse effects were observed that necessitated discontinuation of the study drug. Tolerability of carvedilol was good. All patients except two were treated with the target dose

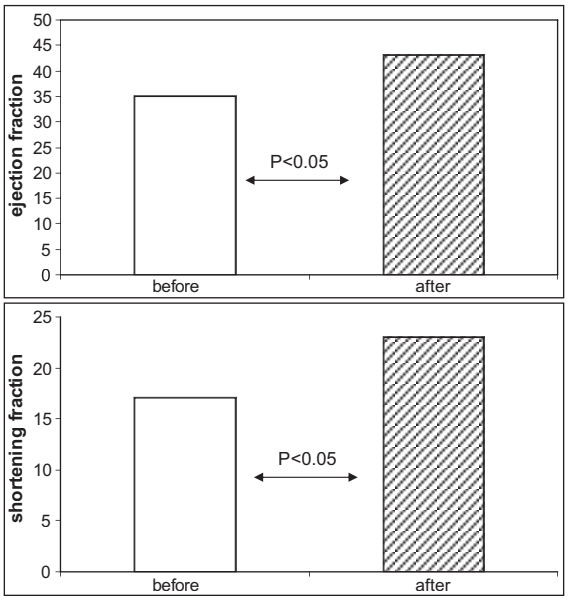

Fig. 1. Change in ejection fraction and fractional shortening before and after carvedilol treatment.

for a minimum of six months. One of the two was unresponsive to the treatment and was lost due to infection and progressive heart failure. The other, however, even with response to the carvedilol treatment, died due to serious infection.

Discussion

The neurohumoral mechanisms of chronic, progressive heart failure involve activation of the sympathetic nervous system and the renin-angiotensin-aldosterone system, leading to intrinsic myocardial dysfunction, apoptosis, and remodeling[8,9]. These pathophysiologic insights led to the hypothesis that β-blockers could prevent this chronic deterioration in patients with heart failure. A remarkable advancement in the treatment of adults with congestive heart failure has been achieved with the significant clinical and experimental evidence that the stimulation of the sympathetic nervous system contributes to the pathophysiology of

Table III. Left Ventricular Systolic Functions of the Study Groups Before and After Carvedilol Treatment

	LVEDD	LVESD	EF	FS
Before	44.3 ± 7.3	38.4 ± 6.7	35.2 ± 6.8	17.2 ± 6.1
After	40.9 ± 6	35.1 ± 5.8	43.1 ± 11.2*	22.7 ± 5.1*

*p<0.05
LVEDD: Left ventricular end diastolic diameter. LVESD: Left ventricular end systolic diameter. EF: Ejection fraction. FS: Fractional shortening.

chronic heart failure[1-4,10]. It is likely that the end-stage pathophysiology in children with progressive cardiac dysfunction is similar, and pediatric patients with heart failure benefit from medicines that have neurohumoral effects such as digoxin and angiotensin converting enzyme inhibitors[11]. However, there are important differences described in children, particularly neonates, which involve cellular mechanisms of calcium regulation and excitation-contraction coupling and physiologic responses relating to β-adrenergic receptors[12,13]. For these reasons, it is important to examine the clinical effect of a therapy such as carvedilol to verify its efficacy in the pediatric population.

Carvedilol is a third-generation β-blocking agent that at therapeutic target doses blocks all three adrenergic receptors that mediate a positive inotropic response in human cardiac myocytes, with a rank of order of potency of $\beta_1 > \alpha_1 > \beta_2$[14]. Because of its α-blocking properties, carvedilol is a moderate vasodilator on acute administration, but with long-term treatment the vasodilator activity is no longer prominent. However, the vasodilator action of the compound contributes to its relatively good initial tolerability because, in contrast to nonvasodilator β-blockers, acute administration of carvedilol does not typically result in profound myocardial depression and clinically important reductions in cardiac output[10].

There are limited data concerning the use of β-blockers in children with ventricular dysfunction. Shaddy[15] first described a group of four children with dilated cardiomyopathy treated with metoprolol with some improvement in function and clinical symptoms. Several other small retrospective studies have shown improved function with limited side effects with the use of metoprolol and carvedilol[16,17]. Some prospective studies, performed by Azeka et al.[18], Laer et al.[7], Rusconi et al.[19] and Blume et al.[13] were also present. Azeka et al.[18] conducted a study of 22 children with severe left ventricular dysfunction (ejection fraction <30%). Eight patients were assigned to receive placebo and 14 patients carvedilol. Initial dose of carvedilol was 0.01 mg/kg/day, and the dosage was doubled at one-week intervals, if tolerated, up to a target dose of 0.2 mg/kg/day and then maintained for at least six months. Significant improvements in ejection fraction and clinical condition of the patients receiving carvedilol were observed. No side effects consistent with carvedilol antiadrenergic actions were seen. Laer et al.[7] had studied 15 patients. The first dose of carvedilol was 0.09 mg/kg/day, and this was increased, as tolerated, up to the maximum adult dose of 50 mg/day. The target dose of 0.70 mg/kg/day had been maintained for at least six months. Improvements were observed after six months of carvedilol therapy in ejection fraction and fractional shortening and no serious adverse effects were seen. Rusconi et al.[19] performed a similar study with 24 pediatric patients with idiopathic dilated cardiomyopathy and left ventricular ejection fraction of ≤40%. Initial dose was 0.15±0.09 mg/kg/day, and this was then increased to a mean maximum dose of 0.98±0.26 mg/kg/day. Mean left ventricular ejection fraction and New York Heart Association functional class were found to be improved. Some of the adverse effects in that study were hypotension, bradycardia, emesis, headache, reactive airway disease and dizziness. In another study, performed by Blume et al.[13], 20 patients with an ejection fraction of less than 40% (12 dilated cardiomyopathy, 8 congenital heart disease) were treated with carvedilol and the results were compared to historical controls. Initial dose was 0.1 mg/kg/day and it was uptitrated to 0.8 mg/kg/day, which was maintained for at least six months. Ejection fraction, compared to untreated controls, was found to be improved significantly from entry to six months. At those dosage protocols, 12 adverse events, in the form of bradycardia, hypoglycemia, and diaphoresis, had occurred in six patients.

This study also prospectively evaluated the use of carvedilol in children with dilated cardiomyopathy. In this study, we have shown that oral carvedilol added to standard drug therapy improved ventricular function and clinical symptom scores in children with dilated cardiomyopathy and moderate-to-severe ventricular function. Carvedilol treatment at this dosage was well tolerated without worsening congestive heart failure in all children but one, who had fractional shortening and ejection fraction of 12% and 28%, respectively, at entry, and of 11% and 17%, respectively, at the time of death, which occurred due to serious infection. In addition, carvedilol was found

to be well tolerated and safe in children with moderate ventricular dysfunction. Our results support the relatively low adverse events in children with structurally normal hearts. Dose escalation was well tolerated in all but two, who ultimately died due to serious infection, and all patients achieved and maintained the highest dose level of carvedilol through the end of the study period. No previously reported side effects were observed.

In this study, the initial carvedilol dose was higher than the one in the study of Azeka et al.[18], but almost the same as those in the study of Laer et al.[7], Rusconi et al.[19], and Blume et al.[13]. The target maintenance dose in this study was higher than that in Azeka et al.'s study[18], but lower than in the others[7,13,19]. The initiation of therapy in our study produced no side effects, so discontinuation of the treatment was not required. Thus, patients were able to tolerate the target doses of carvedilol used. However, it must be emphasized that carvedilol therapy may cause some side effects, and these side effects may be an indicator of maximal therapeutic response. Side effects may be more profound in patients with more severe initial disease as assessed by symptoms and echocardiographic findings. In order to enhance patient safety, in this study, therapy with carvedilol was initiated in small doses that were gradually increased over a period of several weeks.

It is important to note that the impact of carvedilol on survival in pediatric patients with dilated cardiomyopathy cannot be assessed from this study. There are some limitations of the present study. Our data only represent a prospective evaluation of patient care, and no control group is described. In addition, this was not a randomized study. Lastly, with the design of this study, we were not able to measure brain natriuretic peptide plasma levels as a marker of systolic myocardial dysfunction.

In conclusion, our study suggests that oral carvedilol added to standard drug therapy in pediatric patients with dilated cardiomyopathy is well tolerated and associated with an improvement in ventricular function and clinical symptom scores. Carvedilol appears to be well tolerated by pediatric patients of any age, although side effects and concomitant adjustments of other medications should be expected. Therefore, it should be used cautiously with a slow uptitration of dosing as described, and close follow-up of the patients is warranted. Large-scale randomized placebo-controlled multicenter studies will have to be performed to determine the true efficacy of carvedilol on the progression of congestive heart failure, hospitalization rate, and mortality[20].

REFERENCES

1. Lechat P, Packer M, Chalon S, Cucherat M, Arab T, Boissel JP. Clinical effects of beta-adrenergic blockade in chronic heart failure: a meta analysis of double-blind, placebo-controlled, randomized trials. Circulation 1998; 98: 1184-1191.
2. Packer M, Bristow MR, Cohn JN, et al. for the US Carvedilol Study Group. The effect of carvedilol on morbidity and mortality in patients with chronic heart failure. N Engl J Med 1996; 334: 1349-1355.
3. Packer M, Colucci WS, Sackner-Bernstein JD, et al. for the PRECISE study group. Double-blind, placebo controlled study of the effects of carvedilol in patients with moderate to severe heart failure. Circulation 1996; 94: 2793-2799.
4. Colucci WS, Packer M, Bristow MR, et al. for the US Carvedilol Heart Failure Study Group. Carvedilol inhibits clinical progression in patients with mild symptoms of heart failure. Circulation 1996; 94: 2800-2806.
5. Ross RD. Grading the severity of congestive heart failure in infants. Pediatr Cardiol 1992; 13: 72-75.
6. Reithmann C, Reber D, Kozlik-Feldmann R, et al. Post-receptor defect of adenyl cyclase in severely failing myocardium from children with congenital heart disease. Eur J Pharmacol 1997; 330: 79-86.
7. 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.
8. Sabbah HN. Apoptotic cell death in heart failure. Cardiovasc Res 2000; 45: 704-712.
9. Eichhorn EJ, Bristow MR. Medical therapy can improve the biologic properties of the chronically failing heart. Circulation 1996; 94: 2285-2296.
10. Metra M, Nardi M, Giubbini R, Dei Cas L. Effects of short- and long-term carvedilol administration on rest and exercise hemodynamic variables, exercise capacity and clinical conditions in patients with idiopathic dilated cardiomyopathy. J Am Coll Cardiol 1994; 24: 1678-1687.
11. Auslender M, Artman M. Overview of the management of pediatric heart failure. Prog Pediatr Cardiol 2000; 11: 231-241.
12. Ausler M. Pathophysiology of pediatric heart failure. Prog Pediatr Cardiol 2000; 11: 175-184.
13. 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.

14. Yoshikawa T, Port JD, Asano K, et al. Cardiac adrenergic receptor effects of carvedilol. Eur Heart J 1996; 17: 8-16.

15. Shaddy RE. Beta-blocker therapy in young children with congestive heart failure under consideration for heart transplantation. Am Heart J 1998; 136: 19-21.

16. 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.

17. Buckhorn R, Bartmus D, Siekmeyer W, et al. Beta-blocker therapy of severe congestive heart failure in infants with left to right shunts. Am J Cardiol 1998; 81: 1366-1368.

18. Azeka E, Ramires JA, Valler C, Bocchi EA. 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. Shaddy RE, Curtin EL, Sower B, et al. The pediatric randomized carvedilol trial in children with heart failure: rationale and design. Am Heart J 2002; 144: 383-389.