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Efficacy and safety of carvedilol for heart failure in children and patients with congenital heart disease

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Abstract There have been few reports describing the use of carvedilol in children or patients with congenital heart disease. Therefore, its optimal regimen, efficacy, and safety in these patients have not been adequately investigated. Subjects were 27 patients with two functioning ventricles, for whom carvedilol was initiated (from December 2001 to December 2005) to treat heart failure. All patients had failed to respond to conventional cardiac medication. They consisted of 12 males and 15 females, aged 23 days to 47 years (median age: 2 years). Heart failure due to ischemia (myocardial infarction, intraoperative ischemic event) or due to myocardial disease (cardiomyopathy, myocarditis), and heart failure with atrial or ventricular tachyarrhythmia represented 70% of all cases. Carvedilol was initiated at a dose of 0.02–0.05 mg/kg/day, which was increased by 0.05–0.1 mg/kg/day after 2 days, 0.1 mg/kg/day after 5 days, and 0.05–0.1 mg/kg/day every month thereafter with a target dose of 0.8 mg/kg/day. This study retrospectively assessed the efficacy and adverse reactions based on changes of symptoms, cardiothoracic ratio (CTR), left ventricular ejection fraction (LVEF), and human atrial natriuretic peptide (hANP)/b-type natriuretic peptide (BNP) blood levels. The mean follow-up period was 10.2 months (range: 1–46 months). Twenty-six (96.3%) patients showed improvement in symptoms and were discharged from the hospital. However, the remaining one patient failed to respond and died. Significant cardiovascular adverse reaction was seen in none of the patients. The mean CTR decreased from 61.8% ± 5.3% before treatment to 57.6% ± 7.4% after treatment ($P < 0.05, n = 25$), and the mean LVEF improved from 41.4% ± 23.1% to 61.1% ± 10.1% ($P < 0.05, n = 10$), respectively. Mean hANP and BNP levels showed a decrease from 239.1 pg/ml to 118.3 pg/ml and a significant decrease from 437.9 pg/ml to 120.5 pg/ml, respectively ($P < 0.05$, $n = 10$). Improvements in these data were also demonstrated when analyzed individually among the pediatric group (aged younger than 18) and the congenital heart disease group. Initiation of carvedilol at a lower dose with more gradual dose escalation, compared with previously reported regimens, might have efficacy with low incidence of adverse effects in pediatric patients and patients with congenital heart disease. Carvedilol may be effective in treating heart failure in children due to ischemia, myocardial disease, and complicated by tachyarrhythmia.

Key words Carvedilol · Heart failure · Beta-blocker · Congenital heart disease · Children

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Introduction

Heart failure is a state in which the required amount of oxygen is not sufficiently supplied to the vital organs because of reduced cardiac pump function. Recently, it has become evident that various neuroendocrine factors, including the sympathetic nervous system and the renin–angiotensin–aldosterone system, cause aggravation of heart failure. The efficacy of using beta-blocker therapy in adult patients with heart failure due to ischemic heart disease or dilated cardiomyopathy (DCM) has already been demonstrated by various studies, including the U.S. Carvedilol HF Study,[1] the COPERNICUS study,[2] and the CAPRICORN study.[3]

Patients with congenital heart defects often have a history of receiving open heart surgery in the past. Therefore patients have their unique cardiac morphology, which makes uniform evaluation of cardiac function difficult, and various methods have been presented to address each difference.[4,5] It is possible that detrimental influences of the sympathetic nervous system differ between adults and children with heart failure. In addition, children with congenital heart defects often have unique hemodynamic abnormalities such as aorto-pulmonary shunt, which may influence the effect of beta-blocker therapy. There have been several reports[6–13] alluding to the effects of beta-blocker use in

children (including those of Bruns et al.[6] and Laer et al.[7]), but the patient cohort of these reports are small. Also, potential problems due to adverse reactions have been pointed out, including aggravation of heart failure,[9] bradycardia,[9] and hypotension.[6,7,9] Because the appropriate dose of carvedilol, which achieves maximal efficacy with minimal adverse reactions, may differ with patients' age, it is important to determine the most appropriate administration method for children. Several regimens for administration of beta-blockers to children have already been proposed. However, these methods were mainly designed for DCM and there have been few reports on patients with congenital heart disease.

Recently preliminary results suggested that carvedilol does not significantly improve clinical heart failure outcome in patients younger than 18 years with chronic symptomatic heart failure due to systemic ventricular systolic dysfunction.[14] However, our impression had been that carvedilol improve heart failure with children and adolescents. The present study investigated the efficacy and problems associated with the use of carvedilol for children with heart failure, including those with congenital heart diseases with hemodynamic abnormalities.

Subjects and methods

Twenty-seven patients who received carvedilol for treatment of congestive heart failure (from December 2001 to December 2005) were retrospectively reviewed (Table 1). The regimen of carvedilol was determined according to the protocol described in the latter part of this paper. This protocol was modified from the report by Toyono et al.[10] The inclusion criteria were patients younger than 18 years, or with congenital heart defect (CHD). Patients with functional single ventricle and with significant aorto-pulmonary shunt were excluded. There were 12 males and 15 females, with ages ranging from 23 days to 47 years (median age: 2.0 years). Twenty-two of them were pediatric patients (age ≤18 years). Twenty-three patients had congenital heart disease, including 18 pediatric patients. Heart failure due to ischemia (myocardial infarction in 3 and intraoperative ischemic event in 5) or due to myocardial disease (cardiomyopathy in 3 and myocarditis in 1), and heart failure with atrial or ventricular tachyarrhythmia was seen in 19 out of 27 patients (70.4%). The systemic ventricle was morphologically right in 11.1%. All of the patients were

Table 1. Patients' demographics and characteristics

No.	Age	Sex	CHD	Diagnosis	Operation	Indication						Discharge	Follow-up duration
						Tachy	Ischemia	LVD	SRVD	Other	MCD		
1	2 m	F	O	AVSD	ICR	O						O	2
2	2 y	F	O	VSD	ICR	O						O	16
3	6 y	M	O	CoA complex	ICR	O						O	1
4	25 y	M	O	MR	MVP	O		O				O	14
5	27 y	M	O	AVSD	ICR	O		O				O	4
6	32 y	F	O	MR	MVR	O		O				O	3
7	47 y	F	O	TOF	ICR	O		O				O	5
8	23 d	F	O	TGA	ASO		O	O				O	19
9	2 m	M	O	VSD, MR	ICR		O	O				O	3
10	3 m	F	O	DORV	ICR		O	O				O	8
11	3 m	F	O	BWG	Repair		O	O				O	3
12	1 y	M	O	TGA	ASO		O	O				O	21
13	7 y	M	O	TOF, hypoLCA	ICR		O	O				O	3
14	9 y	M	O	ASR	Ross		O	O				O	4
15	10 y	F	O	MR	MVP, MVR	O	O	O				O	13
16	1 y	F	O	TGA(III)	Senning				O			O	1
17	5 y	F	O	TGA(III)	Senning				O			O	13
18	39 y	M	O	LTGA	TVP				O			O	27
19	4 m	M	O	AA	Norwood, Rastelli					O		O	4
20	1 y	M	O	HypoLCA, MSR	None					O		O	15
21	2 m	F	O	Truncus	Rastelli					O		O	5
22	1 y	F	O	AVSD	ICR					O		O	18
23	11 y	M	O	AVSD	ICR					O		X	1
24	3 m	F		NCLVM	None						O	O	7
25	4 m	F		DCM	None						O	O	16
26	3 y	M		DCM	None						O	O	46
27	8 y	F		Carditis	None						O	O	4

d, days; m, months; y, years; Tachy, tachycardia; LVD, left ventricular dysfunction; SRVD, systemic right ventricular dysfunction; MCD, myocardial disease; CHD, congenital heart disease; TGA, transposition of great arteries; OMI, old myocardial infarction; Truncus, truncus arteriosus communis; VSD, ventricular septum defect; MR, mitral valve regurgitation; AVSD, atrioventricular septum defect; DORV, double outlet right ventricle; BWG, Bland–White–Garland syndrome; AA, aortic atresia; hypoLCA, left coronary artery hypoplasia; MSR, mitral valve stenosis and regurgitation; TGA(III), TGA with VSD; CoA complex, coarctation of aorta complex; TOF, tetralogy of Fallot; ASR, aortic valve stenosis and regurgitation; LTGA, corrected transposition of great arteries; NCLVM, noncompaction of left ventricular myocardium; DCM, dilated cardiomyopathy; ASO, arterial switch operation; Rastelli, Rastelli procedure; ICR, intracardiac repair; Norwood, Norwood procedure; Senning, Senning procedure; Ross, Ross procedure; MVP, mitral valve plasty; MVR, mitral valve replacement; TVP, tricuspid valve plasty

hospitalized for the establishment of the treatment. Criteria to initiate carvedilol included symptomatic heart failure resistant to conventional treatment including catecholamines, phosphodiesterase III inhibitors (PDE III-I), diuretics, angiotensin-converting enzyme inhibitors (ACEi), and other cardioactive agents. When carvedilol administration was initiated, patients were on ACEi (19 patients), diuretics (25), digoxin (10), pimobendan (6), intravenous PDE III-I (6), and intravenous catecholamine (4). The median interval between the initiations of ACEi and carvedilol was 4 weeks (range: 1 day to 44 weeks). The mean follow-up period was 10.2 ± 10.1 (range: 1–46) months (Table 1). The efficacy and safety of carvedilol were evaluated as follows.

The efficacy evaluation included symptoms, measurements of cardiothoracic ratio (CTR) on chest roentgenogram, left ventricular ejection fraction (LVEF) on two-dimensional echocardiogram, serum human atrial natriuretic peptide (hANP) level, and serum b-type natriuretic peptide (BNP) level. Evaluation was conducted at a mean of 10.2 ± 10.1 months after the initiation of carvedilol administration, and these measurements were compared with pre-administration values. For safety evaluation, incidences of adverse reactions (aggravation of heart failure, bradycardia, hypotension, vertigo, and death) were assessed. To examine differences in efficacy related to the pathophysiology of heart failure, these parameters were compared among all 27 patients (including 22 pediatric patients: pediatric group; and 23 patients with congenital heart disease: CHD group). Statistical analysis was performed using the paired *t*-test, with $P < 0.05$ being considered significant.

The standard protocol included the initial dose of 0.02–0.05 mg/kg/day, which was increased by 0.05–0.1 mg/kg/day after 2 days, 0.1 mg/kg/day after 5 days, and 0.05–0.1 mg/kg/day every month thereafter with a target dose of 0.8 mg/kg/day. The dose was further adjusted considering the symptoms and individual tolerance.

Results

Dosage of carvedilol

The initial dose of carvedilol was in the range from 0.02 to 0.03 mg/kg/day in 14 patients, 0.04–0.05 mg/kg/day in 11 patients, and 0.1 mg/kg/day in 2 patients. The mean carvedilol dose was 0.04 ± 0.02 mg/kg/day at the initiation of treatment, 0.26 ± 0.16 mg/kg/day at 3 months, 0.23 ± 0.16 mg/kg/day at 4–12 months, 0.43 ± 0.36 mg/kg/day at 13–17 months, and 0.47 ± 0.37 mg/kg/day at 18–46 months (Table 2).

Clinical course

All patients except for one (No. 18 in Table 1) showed improvement of heart failure symptoms and were discharged from the hospital. Five of them were on PDE III-I (including three who were administered catecholamines concomitantly) and were weaned off intravenous therapy.

Changes of CTR and LVEF

The CTR was able to be compared before and after carvedilol administration in 25 patients (20 in the pediatric group and 22 in the CHD group). It showed a significant reduction from 61.8% ± 5.3% to 57.6% ± 7.4% (61.9% ± 5.3% to 57.2% ± 7.5% in the pediatric group, and 61.5% ± 5.3% to 58.2% ± 7.4% in the CHD group; $P < 0.05$). The LVEF was comparable in 10 patients (8 in the pediatric group and 7 in the CHD group). It significantly improved from 41.4% ± 23.1% to 61.1% ± 10.1% (38.1% ± 24.4% to 59.9% ± 11.0% in the pediatric group, and 47.3% ± 20.0% to 59.9% ± 10.4% in the CHD group; $P < 0.05$) (Fig. 1). The degree of atrioventricular valve regurgitation improved in 33%, was unchanged in 52%, and deteriorated in 14% ($n = 21$) after carvedilol administration.

Changes of hANP and BNP

Serum hANP level was compared before and after carvedilol administration in 9 patients (7 in the pediatric group and 6 in the CHD group). The level decreased from 239.1 to 118.3 pg/ml (1271.5 to 139.7 pg/ml in the pediatric group, and 285.5 to 152.7 pg/ml in the CHD group).

Serum BNP level was compared in 10 patients (8 in the pediatric group and 7 in the CHD group). The level significantly decreased from 437.9 to 120.5 pg/ml ($P < 0.05$) (473.9 to 132.7 pg/ml in the pediatric group, and 416.1 to 167.0 pg/ml in the CHD group) (Fig. 2).

One patient showed an increase in hANP and BNP levels after carvedilol administration. This patient was a child with incomplete atrioventricular septal defect who had undergone complete repair. This patient had a residual severe left atrioventricular valvular insufficiency, and did not show any improvement in either CTR or LVEF.

Table 2. Dosage of carvedilol

Initial dosage of carvedilol (mg/kg/day)		Final dosage of carvedilol (mg/kg/day)			
No. of patients	Dosage range	No. of patients	Follow-up duration (months)	Dosage range	Mean dosage
14	0.02–0.03	7	≤3	0.02–0.5	0.26
11	0.04–0.05	8	4–12	0.04–0.5	0.23
2	0.1	5	13–17	0.13–1.0	0.43
		5	18–46	0.10–1.0	0.47

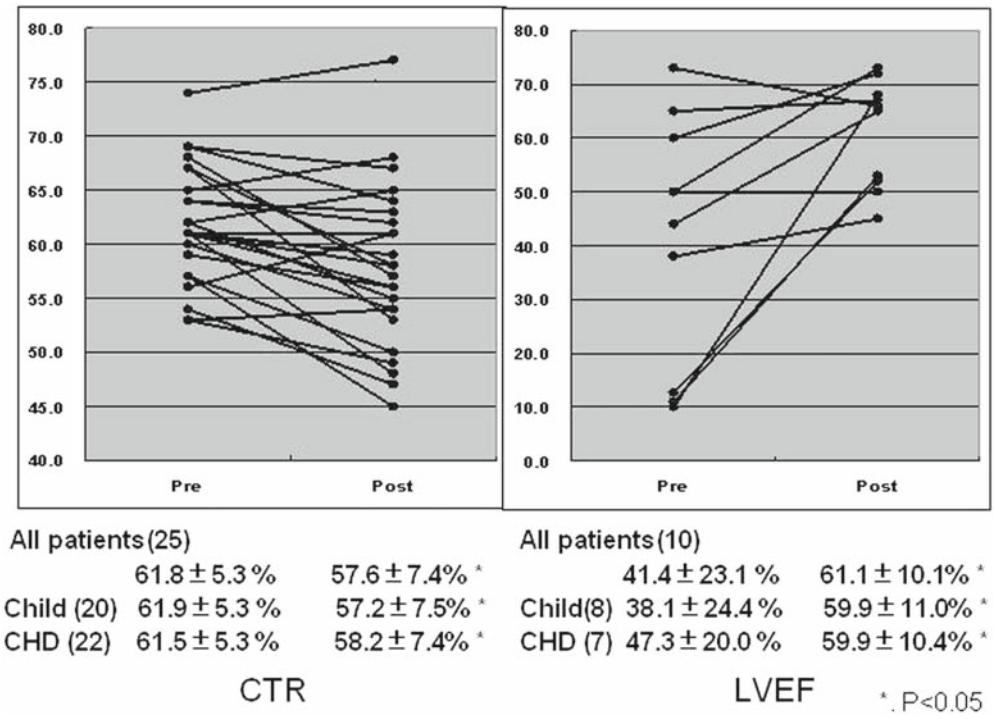

Fig. 1. Change of cardiothoracic ratio (*CTR*) and left ventricular ejection fraction (*LVEF*), pre- and post-carvedilol. The CTR and LVEF were compared before and after carvedilol administration. The CTR showed a significant reduction from 61.8% ± 5.3% to 57.6% ± 7.4% (61.9% ± 5.3% to 57.2% ± 7.5% in child, 61.5% ± 5.3% to 58.25% ± 7.4% in congenital heart defect (*CHD*)). The LVEF significantly improved from 41.4% ± 23.1% to 61.1% ± 10.1% (38.1% ± 24.4% to 59.9% ± 11.0% in child, 47.3% ± 20.0% to 59.9% ± 10.4% in CHD)

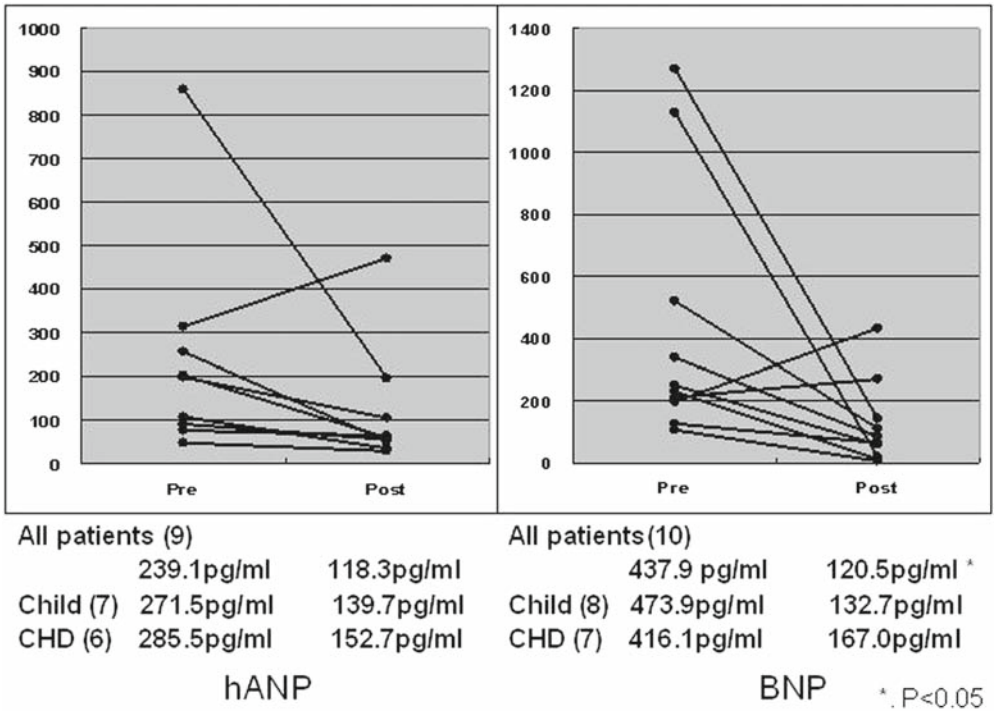

Fig. 2. Change of human atrial natriuretic peptide (*hANP*) and b-type natriuretic peptide (*BNP*), pre- and post-carvedilol. Serum hANP and BNP levels were compared before and after carvedilol administration. The hANP level was decreased from 239.1 to 118.3 pg/ml (1271.5 to 139.7 pg/ml in child, 285.5 to 152.7 pg/ml in congenital heart defect (*CHD*)). The BNP level was decreased from 437.9 to 120.5 pg/ml (473.9 to 132.7 pg/ml in child, 416.1 to 167.0 pg/ml in CHD)

Concomitant drug therapy for heart failure

Twenty-six patients (excluding one mortality case) were assessed. The number of patients using diuretics decreased from 24 to 18 patients. This was possibly a reason for the reduction of side effects. The number of patients using ACEi, pimobendan, and digoxin increased from 18 to 22 patients, 6 to 9 patients, and 10 to 11 patients, respectively. These increments in drug doses were partly attributable to the purpose of enhancing improvement of heart failure. Five patients receiving PDE III-I (including three who were on catecholamines concomitantly) were able to be weaned off these intravenous agents and were discharged from the hospital.

Deaths and adverse reactions

One patient died during the treatment. As was mentioned before, this patient had left atrioventricular valve insufficiency and left ventricular dysfunction after surgery for incomplete atrioventricular septal defect. The general condition was poor before starting this treatment and there was no response to carvedilol. In another patient, carvedilol was changed to atenolol (beta-blocker with greater cardiac selectivity) because of wheezing. No significant adverse reactions related to the cardiovascular system, such as bradycardia, hypotension, or worsening of heart failure, were observed during treatment.

Discussion

In this study, carvedilol caused a respiratory adverse reaction in one patient, but cardiovascular adverse reactions were not seen. Therefore its use for pediatric patients and patients with CHD seemed generally safe. Overall, the efficacy of carvedilol in this study was confirmed with significant improvement in CTR, LVEF, and BNP. Cardiothoracic ratio and LVEF both showed significant improvement in the pediatric and CHD groups. These findings indicate that the carvedilol regimen used in this study is effective for cardiac dysfunctions in these groups.

In previous large-scale studies on the use of carvedilol for heart failure in adults (such as the U.S. Carvedilol HF Study (1996),[1] COPERNICUS (2001),[2] and CAPRICORN (2001)[3]), efficacy was demonstrated and the drug has been considered useful. Use of carvedilol in children has been reported by Bruns et al.,[6] Laer et al.,[7] Williams et al.,[8] Giardini et al.,[9] Toyono et al.,[10] Rusconi et al.,[11] and Azeka et al.[12] However, the numbers of patients in each report were small.

Recently, preliminary results suggested that carvedilol does not significantly improve outcome of patients younger than 18 years with chronic symptomatic heart failure due to systemic ventricular systolic dysfunction.[14] However, our experience showed a possibility that carvedilol improved heart failure with children and CHD. The difference in these outcomes may be attributable to three factors. The first potential factor is the difference in protocol to increase dosage. Shaddy et al.[14] doubled the dosage every 2 weeks. Our protocol included more gradual dose escalation (increase of dosage by 0.05–0.1 mg/kg every month). This difference might also influence the number of patients whose symptoms worsened with carvedilol administration, as is mentioned in the following paragraph. The second factor was the difference in the proportion of patients who had their symptoms worsened by carvedilol administration. This occurred in 25 out of 103 patients (24%) according to Shaddy et al.,[14] and none was seen in our study. This difference might influence the analysis. The last factor is the difference in the study cohort. This study included a significant proportion of patients with ischemia, myocardial disease, and heart failure with tachyarrhythmia for whom other studies[3,11,15] have suggested that carvedilol may be especially efficacious. These patients represented 70% (19 out of 27 patients) in this study. Our study also included a small percentage of systemic ventricle with non-left ventricular morphology for which Shaddy et al.[14] described carvedilol to be less effective. The percentage of these patients was 26% in the study of Shaddy et al.,[14] and 11.1% in our study. In addition, it is possible that our study included patients whose condition might have improved naturally without any medication.

Beta-blockers reduce the load on the heart and are considered to prevent sudden death by inhibition of arrhythmia.[16,17] In addition, carvedilol has a unique feature, such as alpha-1 blocking action, NO-like action,[18] and antioxidant action.[19,20] Therefore, the actions of carvedilol show major differences from those of conventional drugs for heart failure. In pediatric patients and patients with CHD, heart failure involves a complex interaction compared with adult patients, and carvedilol has been found to be especially effective.

However, beta-blocker treatment of heart failure has the risk of causing cardiovascular adverse reactions such as aggravation of heart failure, bradycardia, and hypotension. Therefore the method of administration should be meticulous. Regarding the safety of carvedilol in children, Bruns et al.[6] reported adverse reactions such as vertigo, hypotension, and headache in 54% of patients, while Laer et al.[7] reported adverse events such as vertigo and hypotension in 5 out of 15 patients. Giardini et al.[9] reported that adverse reactions such as bradycardia, hypotension, and aggravation of heart failure were observed. Rusconi et al.[11] reported adverse reactions in 5 out of 24 patients and discontinued administration in two of them. Shaddy et al.[14] reported that symptoms in 25 out of 103 patients (24%) deteriorated with carvedilol administration, with worsened heart failure being the most common adverse event. The administration methods used by these authors are shown in Table 3. In the present study, adverse reactions occurred in only one patient, which represents a very small percentage. The administration regimen used in this study was characterized by a lower initial dose and slower escalation of dose compared with conventional methods. Therefore, adverse reactions such as aggravation of heart failure, bradycardia, and reduction of blood pressure did not occur, and administration could be continued safely.

Reduction in the dose of concomitant diuretic therapy should minimize adverse reactions such as hypotension. On the contrary, ACE inhibitors are often continued concomitantly, because this is expected to improve the prognosis of patients with heart failure[21] and show a synergetic effect with carvedilol.[22] Pimobendan is an oral agent with both cardiotonic and vasodilatory actions that was often initiated when PDE III-I therapy was discontinued in the present study.

Limitations

Limitations to this study include small statistical power due to a small patient cohort, use of other drugs (which could manipulate the effect of carvedilol), and the short follow-up

Table 3. Dosage in childhood

First author[Ref.] (year)	No. of patients	Initial dose (mg/kg)	Method of dose up	Maintenance dose (mg/kg)
Azeka[12] (2002)	22	0.01	0.02 mg/kg, up every week	0.2
Giardini[9] (2003)	9	0.05	Dosage up, every 2 weeks	0.8
Shaddy[13] (2002)	–	0.05	Double dosage up, every 2 weeks	0.4
Bruns[6] (2001)	46	0.08	Double dosage up, every 2 weeks	0.46 (after 11 weeks)
Laer[7] (2002)	15	0.09	Double dosage up, every 2 weeks	0.7
Rusconi[11] (2004)	24	0.15		0.98 (after 14 weeks)
Shaddy[14] (2007)	161		Every 2 weeks	0.2 (low dose) 0.4 (high dose)
This study	27	0.02–0.05	0.05–0.1 mg/kg dosage up, every month	0.8

period; these factors may have significant influence on the results. The determination of the appropriate dose and administration period for carvedilol warrants a larger-scale prospective study.

Conclusion

Carvedilol treatment by the present regimen, with a lower initial dose and slower dose escalation compared with previous regimens, might be safe and effective for pediatric heart failure and heart failure associated with CHD. Carvedilol may be effective in treating heart failure in children due to ischemia and myocardial disease, and complicated by tachycardia.

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