Cardiol Young 2003; 13: 333–336

ISSN 1047-9511

Original Article

Modulation of neurohormonal activity after treatment of children in heart failure with carvedilol

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Abstract *Background:* In adults with heart failure, neurohormonal overstimulation is related to the progression of the disease, and influences prognosis. β-blockers, which modulate neurohormonal activation, now play an essential role in the pharmacological management of heart failure in adults, but their use in children is very limited. *Patients and Methods:* To investigate the effects of carvedilol administration on neurohormonal activation and left ventricular function, carvedilol was added to standard treatment for heart failure in 9 patients with dilated cardiomyopathy due to heart muscle disease. Standard treatment has been in place for at least 1 month. The protocol consisted in a baseline evaluation to assess neurohormonal activation, and echocardiographic evaluation of left ventricular function. This was followed by a final evaluation at 12 months from carvedilol loading. Carvedilol was started at 0.05 mg/kg/day, and increased every two weeks until the target dose of 0.8 mg/kg/day was reached. *Results:* Carvedilol administration was associated with a significant reduction in plasma norepinephrine ($p = 0.00001$), dopamine ($p = 0.0001$), aldosterone ($p = 0.00001$) and activation of the renin-angiotensin system ($p = 0.0006$). Similar reductions in vanilmandelic and homovanillic acid were noted. After 12 months, a positive remodeling took place, with significant reductions in end-diastolic ($p = 0.004$) and end-systolic diameters ($p = 0.009$), and an increase in left ventricular ejection fraction ($p = 0.001$). No adverse effects needing reduction or interruption in the dosage were noted in the run-in phase, nor in the period of maintenance. *Conclusion:* Carvedilol is a safe complement to standard therapy for heart failure in children, allowing a significant reduction of neurohormonal activation with evident benefits on both ventricular function and the clinical condition.

Keywords: β-blockade; cardiomyopathy; cardiac failure

Beta-adrenergic blockade in adults with congestive heart failure has widely demonstrated its efficacy in improving survival, especially if associated with inhibitors of angiotensin-converting enzyme.[1,2] More recently, carvedilol, a new agent featuring both α and β receptor activity, combined with endothelial modulating and anti-apoptotic properties, has been suggested as an even more effective treatment.[3,4] Recent studies have demonstrated significant improvements in cardiac function following administration of the drug in children with heart failure,[5–7] with some of them being de-listed from the waiting list for cardiac transplantation.[8] As far as we know, however, no data has been provided concerning the effects on long- or medium-term prognosis. There is a convincing evidence, nonetheless, that increased neurohormonal activation in adults with heart failure is related to the progression of the disease, with an ominous prognosis.[9,10] In a similar way, children may be expected to improve their clinical conditions by reducing the progression of heart failure by pharmacological modulation of neurohormonal activation. With these aspects in mind, we evaluated the effect of administration of carvedilol on neurohormonal modulation

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Accepted for publication 18 February 2003

and left ventricular function in 9 consecutive children seen in our clinic with severe heart failure.

Patients and methods

Population studied

We evaluated 9 consecutive patients, with a median age of 14.8 months, and a range from 1 month to 11.7 years, seen at our institution from January 2000 to October 2001 with severe cardiac failure. The failure was due to non-compacted myocardium in 2 patients, idiopathic dilated cardiomyopathy in 4 patients, and to dilated cardiomyopathy occurring subsequent to myocarditis in 3 patients. In 5 patients, we carried out serological investigation and myocardial biopsy, including protein chain reaction analysis of myocardial specimens for B 19 Parvovirus. These tests excluded ongoing active viral myocarditis, which was considered an exclusion criterion for the present investigation. Moreover, blood and urinary laboratory tests ruled out any known metabolic or systemic diseases.

Protocol

We performed an initial evaluation in order to assess baseline neurohormonal activation and echocardiographic left ventricular function and dimensions. This was followed by increasing dosage with carvedilol over two months, with a final evaluation performed after 12 months to assess the impact of the drug on neurohormonal activation and cardiac function. The baseline and 12-month evaluations included a clinical assessment, echocardiography with measurement of left ventricular ejection fraction following the protocol of Teicholz, measurements of left ventricular end-diastolic and end-systolic diameters, and an electrocardiogram. Neurohormonal evaluation was performed on collected blood samples to assess levels of norepinephrine, dopamine, and aldosterone in the plasma, evaluation of activation of the renin-angiotensin system, and assessment of urinary homovanillic and vanilmandelic acid.

Treatment with carvedilol was commenced after a stable clinical condition was reached, and after at least 1 month of standard therapy with digoxin, furosemide, and inhibitors of angiotensin-converting enzyme in order to minimise confounding effects related to concomitant treatment with other drugs. Carvedilol was started at the loading dose of 0.05 mg/kg/day, with further up-titration every two weeks until the target dose of 0.8 mg/kg/day was reached, without modification other than adjustments for weight in the other medications. Carvedilol was increased in an in-hospital setting, and patients were discharged after 24 h of clinical and electrocardiographic monitoring to exclude signs or symptoms of carvedilol-related worsening of heart failure.

Table 1. Neurohormonal and ventricular functional changes after 12 months of treatment with carvedilol.

	Baseline	Carvedilol	p
LV end-diastolic diameter (cm/m^2)	6.7 ± 2.2	5.5 ± 2.0	0.004
LV end-systolic diameter (cm/m^2)	4.6 ± 1.9	3.5 ± 1.6	0.009
LV ejection fraction (%)	28 ± 6	47 ± 14	0.001
Plasmatic norepinephrine (ng/l)	914 ± 55	681 ± 150	0.00001
Plasmatic RA (ng/ml/h)	31.5 ± 7.2	21.5 ± 5.7	0.0006
Plasmatic aldosterone (pg/ml)	1242 ± 190	329 ± 151	0.00001
Urinary VMA (mg/g C)	13.7 ± 3.1	6.9 ± 3.9	0.0007
Urinary HVA (mg/g C)	23.9 ± 3.9	10.6 ± 2.9	0.0001
Plasmatic dopamine (μg/g C)	1239 ± 128	412 ± 116	0.0001

Abbreviations: LV: left ventricle; RA: renin–angiotensin system; VMA: vanilmandelic acid; HVA: homovanillic acid

The Wilcoxon matched pairs test was used to compare baseline and follow-up values of neurohormonal and echocardiographic parameters. Comparison of left ventricular diameters was performed after normalization for body surface area. A p value of less than 0.05 was considered significant.

Results

The target dose of carvedilol was reached in all patients during the two-month period of up-titration. In two patients, we noted an increase in atrioventricular conduction delay of up to 240 ms, but this was not considered as justification for down-titration or discontinuation of the drug.

After 12 months of treatment, neurohormonal activation was significantly reduced when compared to baseline values (Table 1). In particular, we found significant reductions in plasma factors bound to neurohormonal activation, including norepinephrine, dopamine, activation of the renin–angiotensin system, urinary vanilmandelic, and homovanillic acid.

Left ventricular ejection fractions (Fig. 1), and left ventricular end-systolic and end-diastolic diameters, had significantly improved after 12 months (Table 1).

No adverse effect needing reduction of the drug, such as severe bradycardia, advanced atrioventricular conduction delays, hypotension or worsening heart failure, was observed either during the period of increased dosage or in the follow-up.

After a mean follow-up of 14.5 ± 4.6 months, only one patient had died. This patient had presented

https://doi.org/10.1017/S1047951103000672 Published online by Cambridge University Press

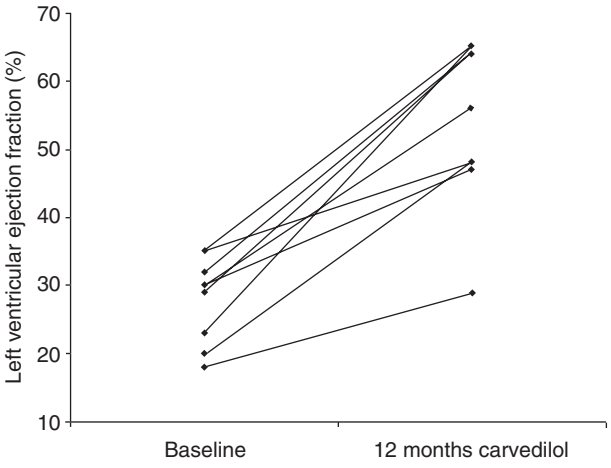

Figure 1.
Changes in left ventricular ejection fraction after 12 months treatment with carvedilol.

with signs of severe heart failure in concert with a viral infection of the upper respiratory tract 17 months after entry to the study. We stopped administration of carvedilol, and instituted intravenous inotropic and diuretic support, but the patient died after five days due to end-stage heart failure and anuria. Another patient underwent successful cardiac transplantation 31 months after entry to the study while receiving carvedilol at 0.8 mg/kg/day.

Discussion

Because of the ongoing shortage of donors, and the significant morbidity and mortality associated with cardiac transplantation in children,[11] continued attempts to optimize medical therapy in children with cardiomyopathy and congestive heart failure are critical.

We have shown that a highly significant reduction in neurohormonal activation, coupled with an improvement in cardiac function, can be achieved following administration of carvedilol for one year in children with heart failure. Thus, carvedilol may be able to block the deleterious effects of chronic neurohormonal overstimulation and, as previously reported,[5–8] might improve cardiac function.

Although a recent consensus statement on management of heart failure in adults[12] recommends that β-blockade now be an integral part of standard regimens for treatment, little data is available on such therapy for children. The remarkable reversal from contraindication to consensus recommendation of β-blockade observed in adults results from an improved understanding of the fundamental pathophysiology of heart failure, and completion of double-blind, randomized, placebo-controlled clinical trials. This improved understanding was largely due to pioneering work on the neurohormonal responses to heart failure and the potentially detrimental effects of long-term activation of the adrenergic nervous and renin–angiotensin systems. In the presence of heart failure, adrenergic stimulation results in increased circulating catecholamines and peptides[13] that, in an acutely beneficial manner, augment heart rate, blood pressure, and myocardial contractility. With time, however, neurohormonal overstimulation can have profoundly detrimental effects on the hemodynamics of heart failure.[14] Direct detrimental effects include myocytic injury and necrosis induced by circulating catecholamines and angiotensin II.[15–17] Additional myocardial loss occurs by adrenergically-mediated acceleration of apoptosis,[18] increase in myocardial consumption of oxygen, and wall stress, with subsequent myocytic damage, fibrosis and worsening cardiac function.[9]

Our data shows that administration of carvedilol was able also to reverse the neurohormonal activation associated with heart failure in children. In particular, carvedilol was associated with a markedly reduced level of circulating plasma noradrenalin, aldosterone and dopamine. The less than expected reduction in activation of the renin-angiotensin system may be correlated to the concomitant use of large doses of diuretics that reduced plasma volume, thus stimulating secretion of renin from the kidney.

In our study, carvedilol was able to produce a significant improvement in left ventricular function, suggesting that a positive remodelling has taken place, as previously demonstrated by Khattar and coworkers in a cohort of adults.[19] In contrast to recently reported data,[7] our 2 patients who were awaiting cardiac transplantation could not be removed from the list. Of these, one died awaiting transplantation, whilst the other was transplanted, and is currently in good health. In this respect, it remains unclear whether treatment with carvedilol will allow a longer survival, or will be able to delay transplantation in such patients. An ongoing multi-centric prospective study is currently evaluating the prognostic impact of carvedilol in such children.[20]

In contrast to what was reported by Buchhorn and coworkers,[21,22] our patients failed to show any significant gain in body weight after 12 months of treatment with carvedilol. The different cause of heart failure in our cases, being due to a cardiac muscle disease and not to simple left-to-right shunting, may give some explanation to this finding.

In our very limited initial experience, carvedilol has proved a safe complement to standard therapy for heart failure in children, allowing a significant reduction of neurohormonal activation with evident

benefits on ventricular function and clinical condition. The effect of carvedilol on survival, and its role in the management of heart failure in infancy, deserves further investigation.

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