

## Case Report

# Efficacy of Carvedilol in the Treatment of Doxorubicin-induced Cardiomyopathy in a Pediatric Patient

Esmail Redha<sup>1</sup>, Sulaiman Alsaad<sup>2</sup>, Ali Alhassan<sup>1</sup>,

<sup>1</sup>Department of Pediatrics, Mubarak Al-Kabeer Hospital, Kuwait

<sup>2</sup>Department of Pediatrics, Al Jahra Hospital, Ministry of Health, Kuwait

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## ABSTRACT

We report a pediatric case with doxorubicin-induced cardiomyopathy that failed to respond to conventional

heart failure medication but improved significantly when placed on carvedilol over a period of one year.

KEYWORDS: carvedilol, congestive heart failure, doxorubicin

## INTRODUCTION

Doxorubicin is an anthracycline used in the treatment of childhood cancer. The most serious long-term side effect of doxorubicin is cardiac toxicity, which can lead to dilated cardiomyopathy (DCM) and congestive heart failure (CHF). The degree of cardiac toxicity is dose-dependent, and the incidence of echocardiographic abnormalities and CHF in children after doxorubicin is significant<sup>[1,2]</sup>. Triple therapy, consisting of digoxin, diuretics and angiotensin converting enzyme inhibitor, is essential in the management of almost all CHF patients. Beta-blockers have been shown to improve symptoms, ejection fraction and survival in adults with congestive heart failure<sup>[3]</sup>. Carvedilol is a unique beta-blocker in that it produces a non-selective beta-receptor and (alpha-1 receptor) blockade, as well as exerts an anti-oxidant effect. Carvedilol was shown to reduce the risk of death as well as the risk for hospitalization for cardiac causes in adult patients with congestive heart failure who were receiving triple therapy<sup>[4]</sup>. There are ongoing studies for the use of carvedilol in children with congestive heart failure. Nevertheless, there are few reports for the use of other beta-blockers, in particular metoprolol, in children with cardiomyopathy and congestive heart failure<sup>[5]</sup>. We report a pediatric case with doxorubicin-induced cardiomyopathy that failed to respond to conventional heart failure medication but improved significantly when placed on carvedilol over a period of one year.

## CASE REPORT

A 5-year old boy with Downs syndrome was diagnosed as a case of acute megakaryoblastic leukemia (AML) type M7, when he presented at the

age of 22 months, with facial swelling that on biopsy proved to be a chloroma. His bone marrow was also infiltrated with AML. He received chemotherapy, which included a total anthracycline dose of 455 mg/M<sup>2</sup>. His echocardiographic evaluations, at baseline and at the end of chemotherapy, were totally normal (left ventricular ejection fraction: 55-65%). He completed his chemotherapy within four months and he was in remission since then.

Approximately seven months after the end of chemotherapy, he started to develop symptoms of CHF including shortness of breath, fatigue, diaphoresis, reduced appetite and poor weight gain. His physical examination was remarkable for resting tachycardia, S<sub>4</sub>, gallop rhythm and hepatomegaly. His chest X-ray showed massive cardiomegaly and his 12-lead electrocardiogram showed biventricular hypertrophy with abnormal repolarization pattern. The echocardiographic evaluations repeatedly showed worsening LV function with an ejection fraction as low as 10% and moderate mitral and tricuspid regurgitation with a right ventricular pressure estimated at 55-60 mm Hg. He required repeated hospitalization for control of CHF, sometimes with intravenous inotropic support. Otherwise, he was maintained on digoxin, lasix and lisinopril. However, his clinical and echocardiographic findings did not show any improvement over a period of one year.

He was then started on carvedilol at a dose of 0.1 mg/Kg/ day in two divided doses which he tolerated very well. His dose was then gradually increased on a weekly basis until he reached his current dose of 1.0 mg/Kg/ day. Shortly after carvedilol was started his clinical status and echocardiographic findings showed significant improvement.

Address correspondence to:

Dr. Sulaiman Alsaad, Al Rawda, P.O.Box 33002, State of Kuwait. Tel: 9736961, Fax: 4577213, E-Mail: sulaimanalsaad@hotmail.com

Fourteen months after initiation of carvedilol therapy, he is asymptomatic with LV ejection fraction as high as 40% and only mild mitral and tricuspid regurgitation with a right ventricular pressure estimated at 40 mmHg. He also needed much less frequent hospitalizations for cardiac issues. We believe from this experience that the introduction of carvedilol to this child's therapy, in addition to conventional heart failure medications had a great impact in improving his overall clinical status.

## DISCUSSION

Structural heart defects are the most common causes of CHF in the pediatric age group<sup>[11]</sup>. Other causes include cardiomyopathies due to inherited disorders such as some inborn errors of metabolism or acquired as in viral or toxin-induced myocarditis<sup>[12,13]</sup>. The medical therapy of CHF has evolved tremendously over the last two decades. Multiple regimens have been used in CHF management including digoxin, ACE inhibitors, and diuretics<sup>[11]</sup>. Most recently, specific beta blockers have been recommended for addition to such regimes. The most recent digitalis investigation group (DIG) trial has provided strong evidence of improved morbidity in congestive heart failure treatment in adult patients using digoxin<sup>[14]</sup>. On the other hand, there are only a few reports in children showing some benefits of digoxin in CHF in small non-randomized or unblinded trials<sup>[15-17]</sup>. Moreover, in the most recent DIG trial subgroup study, digoxin therapy had no effect on the health related quality of life in patients with heart failure in sinus rhythm<sup>[18]</sup>.

Because of their negative inotropic effects, betablockers were thought for many years to be contraindicated in patients with heart failure<sup>[6]</sup>. However, we now know that the course of chronic heart failure can be adversely influenced by neurohormonal activation and the increase in sympathetic tone can potentiate the activity of renin-angiotensin in such patients, leading to retention of salt and water, arterial and venous constriction, and increased ventricular preload and afterload<sup>[7]</sup>. Excess catecholamines as well can increase the heart rate and cause coronary vasoconstriction, thereby diminishing myocardial blood flow<sup>[8]</sup>. These findings have led to the evaluation of betablockers in patients with CHF and indeed, a decrease in sympathetic tone and increase in vagal tone may contribute to the protective effect of beta blockers<sup>[9]</sup>.

In the 1990s, a new drug, carvedilol raised a great deal of interest. It is unique among betablockers in that it exerts a nonselective betareceptor and alpha-1 receptor blockade in

addition to its antioxidant effect. In a double blind, placebo-controlled trial, carvedilol was shown to reduce the risk of death as well as the risk for hospitalization for cardiovascular causes in adult patients with CHF who were receiving therapy including digoxin, diuretics and ACE-inhibitors<sup>[4]</sup>. Although betablockers such as propranolol and metoprolol improve symptoms and left ventricular function, they have not been effective in improving survival in patients with CHF<sup>[10]</sup>. Thus, it is possible that the beneficial effects of carvedilol may be secondary to its antioxidant effect. There are few reports about the use of betablockers, in particular metoprolol, in children with cardiomyopathy and CHF<sup>[5]</sup>. Most recently there were some multicenter randomized trials for the use of carvedilol in the treatment of CHF in children, which showed that Carvedilol as an adjunct to standard therapy for pediatric heart failure improves symptoms and left ventricular function as assessed by echocardiography<sup>[19,20]</sup>. Our experience with this patient illustrates how conventional heart failure therapy alone, failed to improve the clinical status, while the addition of carvedilol induced a significant impact on his heart failure.

In conclusion, knowing that dilated cardiomyopathy is the primary indication for heart transplantation in children beyond infancy and because of the ongoing donor shortage and the significant morbidity and mortality associated with heart transplantation, it is of utmost importance to optimize the studies involving carvedilol to prove its efficacy and safety in the pediatric population with cardiomyopathy and CHF.

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