

## Phosphodiesterase Inhibition in Pediatric Heart Failure – Beneficial or Detrimental? Comparison to Adults with Heart failure

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### Pediatric Heart Failure Due to Idiopathic Dilated Cardiomyopathy

Dilated cardiomyopathy (DCM) is the most common cause of heart failure (HF) in children and carries a poor clinical prognosis; within one year of diagnosis, nearly one third of pediatric patients with DCM either die or undergo heart transplantation [1]. DCM is a heterogeneous group of myocardial diseases characterized by cardiac dilatation and impaired myocardial contractility [2]. In the pediatric population, etiologies of DCM include inflammatory disease (myocarditis), familial or genetic disease, neuromuscular disorders, toxins (anthracyclines), and inborn errors of metabolism. However, the majority of pediatric DCM remains idiopathic in nature – idiopathic DCM comprised 66% of DCM patients from the Pediatric Cardiomyopathy Registry [1].

The unknown etiology of DCM in a large proportion of pediatric DCM patients has consequently limited the advancement of disease-specific medical therapy. Additionally, outcomes studies in pediatric DCM are limited inherently by small numbers. Thus treatment of children with idiopathic DCM has largely mirrored that of adults with idiopathic DCM. Numerous clinical trials in adult patients have clearly demonstrated that inhibition of the renin-angiotensin-aldosterone system and beta-blockade of sympathetic nervous system activation result in substantial reduction in mortality and symptomatic improvement among adults with HF [3,4]. While there is significant variability among centers and among functional class, children with idiopathic DCM are treated with: anti-HF therapy (digoxin and diuretics, 87%), ACEi therapy (70%), and BB therapy (18%) [5]. However, despite the application of ACEi and BB therapies to children with idiopathic DCM, a recent review suggests that pediatric patients with idiopathic DCM do not benefit from these therapies to the same extent as adults [6]. Specifically, in a

multicenter, double-blind, placebo-controlled trial of pediatric patients with HF, the BB carvedilol was not associated with an improvement in survival when compared with placebo [7]. Furthermore, there is differential adaptation of the beta-adrenergic receptors and adrenergic signaling pathways in children with HF when compared with adults, suggesting that age-related differences in adaptation could influence response to therapy [8]. In fact, no substantial improvement in survival has been observed in children with DCM over the past three decades [6]. Five-year freedom from death or transplant remains low at 54%-63% [1,6,9,10]. This differential response to pharmacotherapy suggests that the pathophysiology of HF due to pediatric DCM is a different from adult DCM, emphasizing the need for pediatric-specific investigation and treatment.

### Milrinone Use in Pediatric Heart Failure

Since current medical therapies have not resulted in a substantial reduction in mortality nor obviated the need for heart transplantation, the use of intravenous inotropic support for pediatric patients with DCM has remained necessary. Milrinone, a phosphodiesterase 3 inhibitor, is often employed due to its ability to improve myocardial performance without raising myocardial oxygen consumption [11,12] or increasing afterload [13]. Based on animal models and adult trials, milrinone increases inotropy as a result of cAMP-mediated increase in trans-sarcolemmal calcium flux [14], peripheral vasodilation by increased uptake of calcium into the sarcoplasmic reticulum [15-17], and increased lusitropy from a mechanism probably related to improved actin-myosin dissociation during diastole [18]. Pediatric studies surrounding PDE inhibitor use have primarily focused on milrinone use following congenital heart surgery in order to prevent low cardiac output syndrome [19-26]. However, numerous adult studies have documented beneficial, short-term hemodynamic effects of PDE3 inhibitors in adult patients with HF [27-31] and milrinone use has been extrapolated to pediatric DCM with severe HF.

Nevertheless, despite acute hemodynamic benefits, clinical trials in adults with severe HF have shown that short-term (48 to 72 hours) PDE inhibitor treatment did not decrease the number of days hospitalized, in-hospital mortality, 60-day

mortality, or re-admission [32-33], and tolerance, in the form of decreased levels of cAMP, may develop when treatment is extended [34]. A randomized, placebo-controlled trial of low-dose oral enoximone (another PDE3 specific inhibitor) in adults did not show improvement in any major clinical outcomes [35]. Additionally, multiple studies have shown trends toward increased transient ventricular arrhythmias associated with the use of milrinone, ranging in incidence from 12.2% - 16% [30,36]. Long-term oral PDE inhibitor therapy in adults with NYHA Class III and IV HF was studied in the Prospective Randomized Milrinone Survival Evaluation (PROMISE), which showed that when compared with placebo, milrinone increased cardiovascular mortality by 34% and increased hospitalizations [37].

Despite the adult data, intravenous milrinone is still routinely used in pediatric patients hospitalized for HF exacerbations with seemingly sustained hemodynamic benefit. Furthermore, at several institutions including our own, intravenous milrinone has been continued on an outpatient basis for some “inotrope-dependent” pediatric patients with idiopathic DCM who are listed for transplantation and awaiting a suitable organ [38,39]. In a review of the pediatric patients who underwent heart transplantation at the Children’s Hospital Colorado since the year 2000, 94 patients were on milrinone as a bridge to transplant and 56% of these patients were receiving milrinone infusions at home (outpatient therapy). In contrast to the adult experience, none of these patients on milrinone experienced sudden, unexpected death. Of note, none of the pediatric patients treated with milrinone at our Institution developed new arrhythmias while on treatment. Due to the disparate clinical findings between children and adults with HF treated with PDE inhibitor (namely sustained hemodynamic benefit and decreased arrhythmia risk in children), it is likely that there are differences between pediatric and adult cardiac PDE systems and their responses to chronic PDE inhibitor therapy. Unfortunately, the intravenous administration of milrinone and the detrimental results observed in clinical trials in adults, prevent the long-term treatment of pediatric patients with PDE3 inhibitors. Although the addition of PDE3 inhibitor treatment to standard oral medications for children with heart failure is safe in the outpatient setting, results in fewer heart failure emergency department visits, fewer cardiac hospital admissions and improved NYHA classification [39], due to the lack of controlled clinical trial data for PDE3 inhibitor treatment in children with heart failure, there remains some controversy regarding its routine use in this setting. As a result, PDE3 inhibitor treatment is discussed in the pediatric HF treatment guidelines, but no formal recommendation is provided [40]. Future studies demonstrating the safety of milrinone treatment in a larger pediatric HF population, and the molecular mechanisms responsible for the observed differences in adults and children with HF are necessary, and may result in the development of oral PDE3 inhibitor treatment for long term therapy of pediatric HF patients.

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