CALCIUM SENSITIZING AGENTS IN HEART FAILURE CHILDREN

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Summary

Treatment of heart failure in pediatrics patients is challenging now a days. Administration of these medications sometimes produces disastrous results due to underdeveloped enzymes in children as experience with chloramphenicol and "gray baby" syndrome has demonstrated. Finally, the process that allow excretion of medications in adult patients are still under development in infants, possibly resulting in supratherapeutic concentrations of drugs and unwanted side effects. This review focuses on new and emerging therapies for heart failure that have relevance in infants and children at present or near future. The latest advances in the medications for heart failure are being developed in adults, and the round judgment and experience of the clinician are required to apply three medications safely and appropriately in pediatric patients with heart failure. Calcium sensitizing agents represents a new frontier in treatment of acute decompensated heart failure and may replace traditional ionotropic therapies. Vasopressin antagonists and tumour necrosis factor inhibitors are also targeting aspects that are currently not completely understood. Administration of these therapies to pediatric patients will require carefully scrutiny of the data and skilled application.

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Introduction

A keen knowledge of pathophysiology and pharmacology is necessary to adequately treat pediatric patients with heart failure. Development of these agents for children tends to be more difficult due to the smaller number of patients with heart failure. Rapid developmental changes occur in childhood that can create varying effects on drug pharmacokinetics and pharmacodynamics [1]. Parameters such as gastric pH, drug metabolizing enzymes, intestinal motility, gastric emptying time and volume of distribution altering with age. Due to small amount of data that are available, approximately 75% of prescription medications have inadequate information regarding pediatric use [2, 3]. Heart failure represents a complex interrelation ship between neurohumoral and heamodynamic mechanisms. Mainly it is due to "myocardium failing to meet the metabolic demands of body". [4]

Drugs which are commonly used for in heart failure are, positive ionotropes, aldosterone antagonists, β-blockers, diuretics, vasopeptidase inhibitors play fundamental role in managing heart failures. Introduction of such newer agents such as levosimendan, improve calcium handling and may incur less damage to the myocardium [6].

The use of standard inotropes, such as milrinone and dobutamine, has been shown to be detrimental to the myocardium resulting in intracellular calcium levels and cellular apoptosis [5].

Tumor necrosis factor has long played a role in decompensated heart failure, decreasing the cardiac function of adult patients with sepsis [7].The vaso constriction and anti diuretic and natridiuretic effects of vasopressin are also being targeted in the treatment of heart failure, as serum levels of vasopressin are often elevated in patients with myocardial dysfunction[8]. The best available data for these agents follows, and the expert clinical application of this data is of at most importance.

Calcium Sanitizing Agents

There has been considerable interest in the development of these agents, which may be due to their unique mechanism of action. By prolonging the effects of calcium in the myocardium they are useful in heart failure, but do not affect the levels of calcium in myocardium, this may lead to decreased incidence of arrhythmias from calcium overload [9].

Levosimendan is a calcium sensitizing agent, it is having positive chronotropy, positive ionotropy and vasodilatory effects without increase in myocardial oxygen consumption [10]. It acts by binding to calicium saturated troponin c complex and stabilizes the troponin C-complex and stabilizes the troponin C-calcium complex without affecting the initial calcium binding capabilities of troponin-C. This allows for a longer half life and more effective utilization of calcium in the myocardium, without increasing cytosolic calcium concentrations [11]. Levosimendan has shown benefit in adult patients with congestive heart failure, resulting in increased cardiac output, decreased pulmonary capillary wedge pressure and improvement in symptoms. The vasodilatory effects (including coronary arterial vasodilation) of levosimendan are due to the opening of adenosine triphosphate - sensitive potassium channels in vascular smooth muscle cells [12, 13, 14, 15]. The opening of the potassium channels results in antistunning effects on the myocardium [16]. Continuous infusions of levosimendan at doses of 0.1-0.4 μg/kg/min increased cardiac output and stroke volume, with only slight increase in heart

rate. These infusions also resulted in decreased coronary, pulmonary, and peripheral vascular resistance [17, 18].

Oral levosimendan has been studied in patients with NHYA class III or IV heart failure due to coronary artery disease or dilated cardiomyopathy. Eight of these patients were being treated with a β- blocker and five were being treated with a long acting nitrate. Single doses of 1 and 4 mg of levosimendon resulted in significant decrease in pulmonary capillary wedge pressure (PCWP) and right arterial pressure, and they also resulted in significant increase in cardiac output. Because these were one-time doses, the effect of continuous dosing could not be described [19].oral levosimendan has also shown benefit in weaning patients with severe heart failure from ionotropic therapy [20].

Several clinical trials with levosimendan in adults have been performed. The calicium sensitizer or inotrope or none in low output heart failure study (CASINO) compared levosimendan with doubatamine and placebo in adult patients with decompensated heart failure. The trail was stopped before 50% of the patients could be enrolled in the composite end point of death or rehospitalization due to heart failure. Six month mortality for levosimendan was 18%, which was stastically less than 28.3% for placebo and 42% for dobutamine [21].

Dobutamine was compared with levosimendan in the LIDO study, which enrolled adult patient with low output heart failure. An initial loading dose of 24mg/kg of levosimendan, followed by an infusion of 0.1mg/kg/min, was administered 103 patients. In 100 patients, dobutamine was infused at a dose of 5mg/kg/min for 24hrs with no loading dose. Five patients in the levosimendan group and 6 in the dobutamine group had dose limiting events leading to the temporary discontinuation of the medication. Overall 47% levosimendan patients had adverse events, compared to 42% in the dobutamine group. The primary hemodynamic end point was achieved in 28% of the levosimendan patients and 15% of the doutamine patient. At 180 days, 26% of the levosimendan patients had died,compared to 38% of the dobutamine patients. At 180 days, 26% of the levosimendan patients had died compared to 38% of the dobutamine patients. These statistically significant percentages led the authors to conclude that levosimendan may be better choice than dobutamine for severe low output heart failure [22].

In case of pediatrics, only few studies and reports are available. It was found that the pharmacokinetic parameters of levosimendan is same for adults and children except,patients 3-6 month age had a lower terminal half life. A 2 month old infant received levosimendan for acute heart failure after cardiac surgery and had subsequent improvement in left ventricular function [23]. A 12 year old female with acute dilative cardiomyopathy and placed on a ventricular assist device, levosimendan was started and significant improvement was noted in shortening fraction over the next 5 days [24].

Further data and experience of levosimendan in treating the heart failure in adults and children is necessary.

Conclusion

Different pharmacological strategies such as dopamine-β-hydroxylase inhibition, apoptosis inhibition, G-protein coupled receptor modifiers, intracellular signal transduction pathway modifiers and even gene therapy will yield potential drugs in the future for the treatment of heart

failure in both adults and children. Optimal results in adults are usually a precursor for investigation of a new agent in pediatrics. It is suggested that calcium sensitizing agent lesosimendan acts better compared to dobutamine and other agents as suggested by different clinical trials. But case reports of adverse events from decreased metabolism of drugs are available but offer little proactive insight into pediatric pharmacotherapy. Investigation into this area of the pharmacological treatment will undoubtedly result in improved care for pediatric patients with heart failure.

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