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Case Report

Levosimendan. A promising future drug for refractory cardiac failure in children?

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ABSTRACT

Intravenous positive inotropic agents play an important role in treating acute decompensation of patients with heart failure due to left ventricular systolic dysfunction. Levosimendan is a new positive inotropic agent having ATP-dependent potassium-channel opening, and calcium-sensitizing effects, which increases cardiac contractility and performance along with vasodilatatory action without increasing myocardial oxygen demand. We report a case of a 12-year-old girl with viral myocarditis, dilated cardiomyopathy, biventricular failure with severe left ventricular dysfunction, refractory to standard management, and who was successfully improved with levosimendan.

1. Introduction

Levosimendan is a new pyridazinone-dinitrile derivative with positive inotropic effects belonging to the category of ''inodilators'', which increases cardiac contractility and performance along with vasodilatatory action. It is a calcium-sensitizing drug, which causes vasodilatation by opening ATP-sensitive potassium channels without increasing myocardial oxygen demand.[1,2]

We present a case of viral myocarditis with dilated cardiomyopathy, biventricular failure, severe left ventricular dysfunction, and refractory to standard management, which successfully improved with levosimendan.

2. Case report

A 12-year-old girl, previously healthy, presented with moderate to severe grade fever since 10 days. Following this, the child developed abdominal pain and breathlessness, NYHA GRADE-1, since 7 days. Breathlessness increased progressively and on admission it was associated with orthopnea. The child received symptomatic treatment from a local doctor. The child had chest pain since 2 days and was referred to our hospital. There was no history of any previous cardiac problem, breathlessness, seizures, trauma, bluish discoloration, tubercular contact, or hospitalization. On admission, vital signs were as follows: pulse: 140/min, regular rhythm, low

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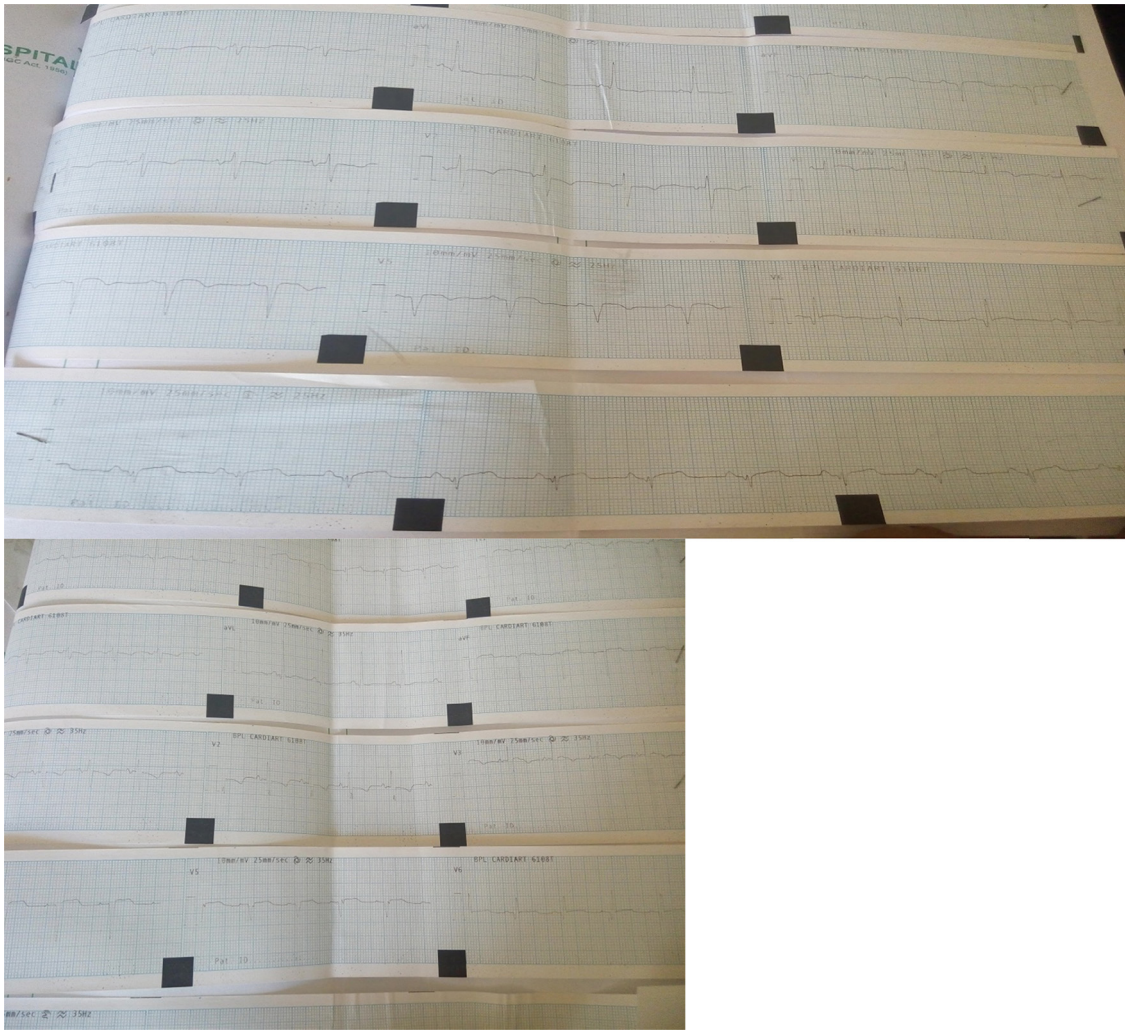

Figs. 1 and 2 – Nonspecific ST and T wave segments, suggestive of myocarditis.

volume, all pulses were felt but weak and thready; B.P: 110/84 mmHg; respiratory rate: 44/min; SpO_2: 96% at room air. Child had mild pallor, bilateral pitting pedal edema and raised JVP. Cardiovascular system examination revealed cardiomegaly and S3 gallop without any murmurs. Child had bilateral fine basal crepitations in chest with mild hepatomegaly. On admission, all routine blood and urine investigations were normal. Serum creatine kinase MB, Se. lactate, and Se. troponin were high and were 74 units/L, 4.5 mmol/L, and 2.3 ng/mL, respectively. ECG was suggestive of features of myocarditis. ECHO was done that was suggestive of dilated cardiomyopathy, and biventricular failure with severe left ventricular dysfunction with ejection fraction of only 15%.

Child was started on oxygen inhalation, iv fluids, dobutamine, Lasix, digoxin for DCM, and antibiotics and was monitored strictly. Carvedilol and enalapril were added on 2nd day as there were no signs of improvement. Cause of cardiomyopathy could never be established. On 2nd day, child developed supraventricular tachycardia and diltiazem was started. In view of ischemia heparin, aspirin and clopidogrel were started. As ejection fraction did not improve even after 3 days of dobutamine, levosimendan infusion was started and dobutamine was tapered and stopped. Patient improved gradually. On 6th day LVEF improved up to 35%. Heparin was stopped after 5 days and rest of the drugs were continued (Figs. 1–3).

3. Discussion

Main aim for reporting this case is that novel drug levosimendan can be used in refractory cardiac failure with low ventricular function.[3] Improvement after levosimendan was remarkable. Oxygen, catecholamines, inotropes, phosphodiesterase inhibitors, diuretics, and drugs for afterload reduction are still the basis for cardiac failure.

Levosimendan is a novel drug that acts as a myofilament Ca^{2+} sensitizer by acting on troponin with inotropic effects, increases myocardial performance without substantial changes in oxygen consumption, causes myocardial oxygen

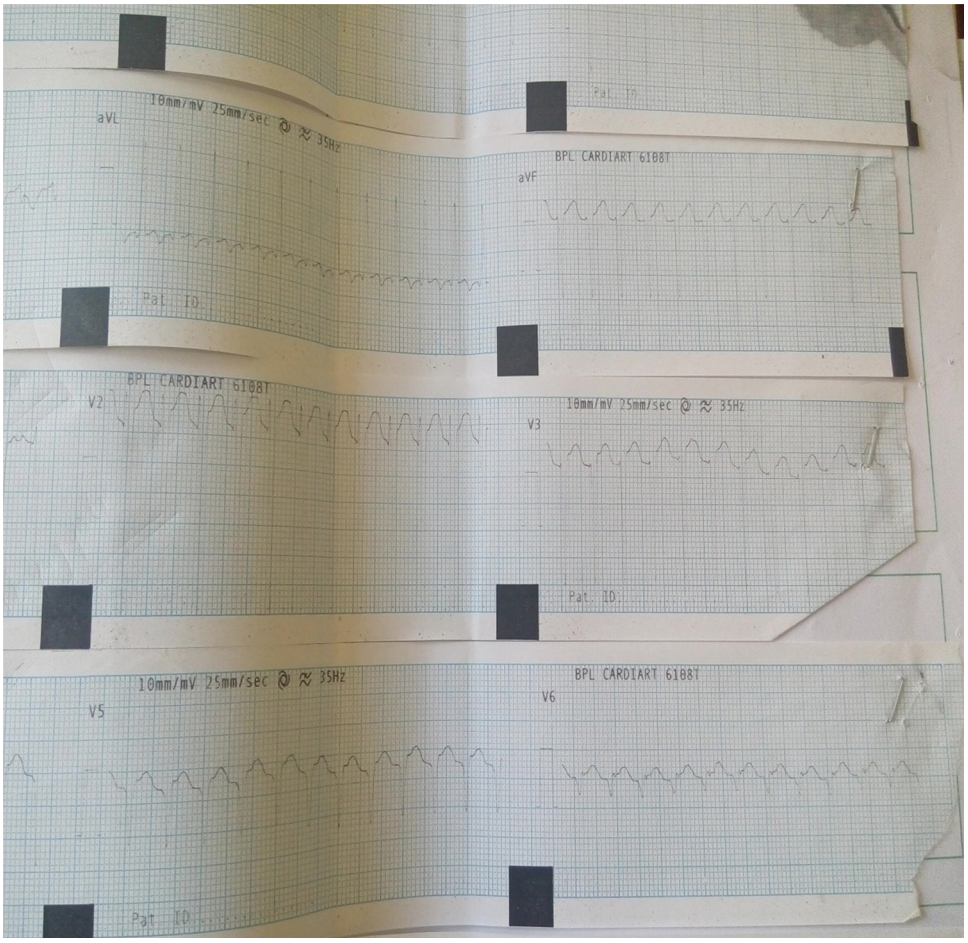

Fig. 3 – Features suggestive of supraventricular tachycardia.

demand, and is with neutral effects on heart rhythm. It is 98% bound to plasma proteins and completely metabolized prior to excretion. Approximately 5% of the dose is converted in the intestines to a highly active metabolite with an elimination half-life of 75–80 h (compared to 1 hour elimination half-life for levosimendan itself). This metabolite reaches a peak plasma concentration in about 2 days after the termination of the infusion and exhibits hemodynamic effects similar to those of levosimendan. Because of the long half-life of the active metabolite, these effects last for up to 7–9 days.[4] A wide range of levosimendan doses has been reported in critically ill patients with doses differing significantly between studies (bolus 0–24 μg/kg, continuous infusion 0.05–0.2 μg/kg/min).[5]

Levosimendan opens both mitochondrial and sarcolemmal Potassium ATP channels and is anti-ischemic with vasodilatory actions. In contrast to catecholamines and phosphodiesterase-3 inhibitor, the potential for arrhythmia is also reduced as total intracellular calcium levels are not raised but sensitizes myofilaments to calcium. The stabilization effect is calcium dependant and levosimendan exerts its effects during systole; it does not effect the duration of diastole and so ventricular relaxation is not impaired. Consequently, adequate ventricular filling and optimal coronary perfusion still occurs. Levosimendan has also been used in pulmonary vasoconstriction and right ventricular dysfunction and reduces pulmonary vascular resistance.[6] In few clinical trials comparing levosimendan versus dobutamine and milrinone infusions in heart failure, levosimendan led to greater improvement in hemodynamics and it was associated with a lower risk of death at 31 and 180 days.[7]

In adults, the role of levosimendan is definitely established. Till now, there are only few studies regarding usage of levosimendan in children in the perioperative period with normal left ventricular function to maintain cardiac output.

In one study in children, levosimendan allowed for substantial reduction in catecholamine infusions with end-stage or acute heart failure and also produced an objective improvement in myocardial performance in acute heart failure.[8]

In another study, the administration of levosimendan in seven infants with severe myocardial dysfunction was well tolerated intraoperatively. The mean arterial lactate levels declined. Central venous oxygen saturation increased significantly 24 and 48 h after the onset of levosimendan infusion.[9] In addition to its inotropic and vasodilator effects, levosimendan has several other important effects, including anti-inflammatory effects and anti-apoptotic effects.[10]

4. Conclusion

The current best evidence suggests that levosimendan is beneficial in improving cardiac performance and reducing the left ventricular afterload. In addition, it may be effective in reducing the need for catecholamine infusions and the duration of critical care. Furthermore, it is safe and well tolerated. It is a promising rescue drug for a potential clinical benefit in low-cardiac output and postcardiac surgery patients. No data are available to validate its role with regard to its cost effectiveness in comparison with milrinone. These encouraging results need to be evaluated by larger, well-designed clinical trials and its indications further elucidated. However, the present evidence may not be enough to recommend it to change the current practice in pediatrics.

Conflicts of interest

The authors have none to declare.

Author contribution

K.S. and K.A. were involved in the acquisition, analysis and drafting the manuscript, critical revision of the manuscript and K.S. and S.S. revised final approval of the version to be published.

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