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Brief Report

The use of levosimendan in children with cancer with severe acute cardiac dysfunction: case series and a review of the literature

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Abstract We report the use of levosimendan in two febrile, neutropenic children with cancer – one post bone marrow transplant – with acute heart failure following chemotherapy. Initial management with epinephrine, milrinone, and diuresis was unsuccessful. Infusion of levosimendan without a loading dose was added to the ongoing heart failure therapy, which resulted in persistent symptomatic and echocardiographic improvement without major side effects.

Keywords: Levosimendan; heart failure; chemotherapy; bone marrow transplantation; children

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Levosimendan is a calcium sensitiser that binds to calcium-saturated Troponin-C, stabilising and prolonging its interaction with Troponin-I, therefore improving contractility without impairing diastolic function and without increasing myocardial oxygen consumption. It also has vasodilator effects – pulmonary, coronary, and systemic – related to the opening of adenosine triphosphate-sensitive K^+-channels and hyperpolarisation of vascular smooth muscle cells.[1] Levosimendan has linear pharmacokinetics and a short half-life of 1–1.5 hours, but its active metabolite (OR-1896) has a half-life of 70–80 hours, even after the discontinuation of a 24-hour infusion.[1] Side effects include headache, hypotension, dizziness, nausea, and tachycardia.[2]

Levosimendan efficacy in heart failure is still controversial. Early, large multi-centre studies have shown a significant decrease in mortality when compared with placebo or dobutamine (LIDO, CASINO, RUSSLAN), but further studies have not shown any benefit (REVIVE, SURVIVE).[3] Recently, two meta-analyses in adults have shown that levosimendan improves haemodynamics and decreases mortality in comparison with dobutamine, although one of them failed to show a survival benefit.[4,5]

We have described the clinical and haemodynamic improvements gained after levosimendan infusion in two children with cancer who developed acute heart failure after chemotherapy.

Case A

A 4-year-old girl with a recent diagnosis of acute myeloid leukaemia was admitted to the Pediatric Intensive Care Unit with respiratory distress. After chemotherapy, she had developed neutropenia and sepsis – *Escherichia coli* in blood cultures – for which she was started on broad-spectrum antibiotics. Subsequently, she developed progressive respiratory distress. At this time, she had already been treated with antibiotics for 4 days and was not hypotensive. An echocardiogram showed a dilated left ventricle with severely reduced function (left ventricular ejection fraction 27–30%). Investigations for myocarditis were negative for viral infections or reactivations. On admission to the unit, she was tachycardic (heart rate 160–170 bpm) and with systolic blood pressure in

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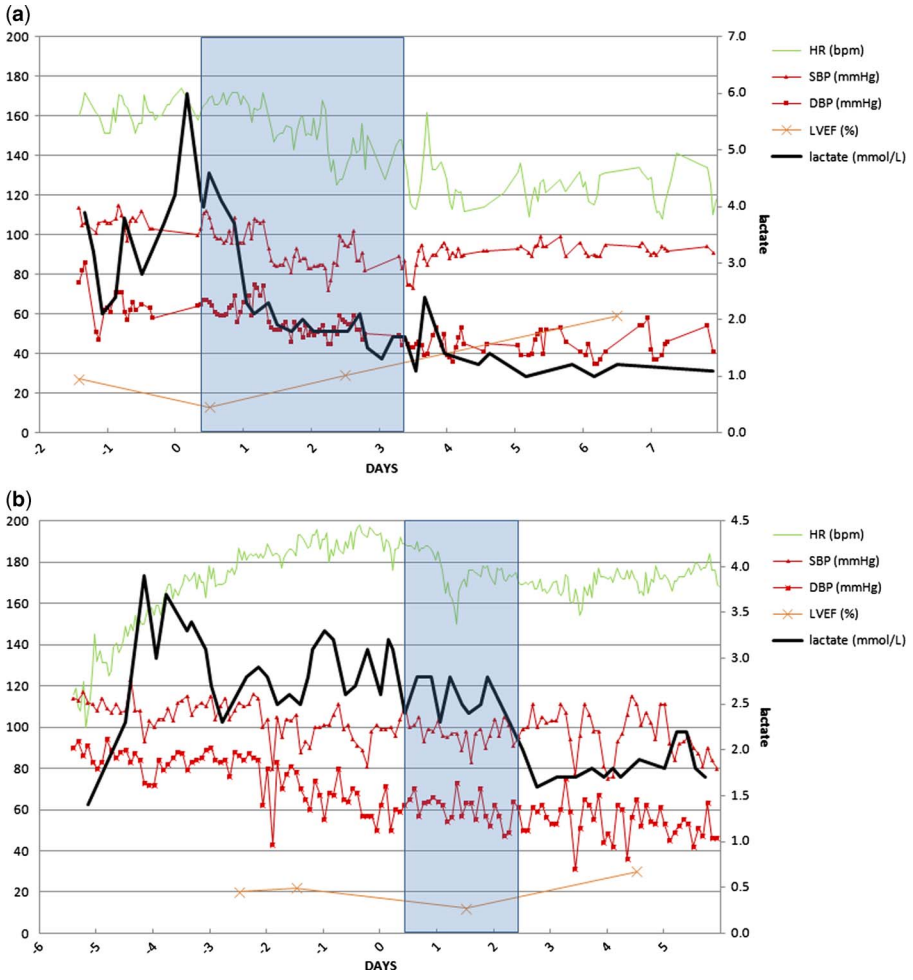

Figure 1.
(a) Case A: haemodynamic data, serum lactate, and ventricular function (LVEF) since admission, with day 0 being the day when levosimendan was started. The shadowed area represents the timeframe of levosimendan infusion. (b) Case B: haemodynamic data, serum lactate, and ventricular function (LVEF) since admission, with day 0 being the day when levosimendan was started. The shadowed area represents the timeframe of levosimendan infusion. DBP = diastolic blood pressure; HR = heart rate; LVEF = left ventricular ejection fraction; SBP = systolic blood pressure.

100–115 mmHg range, in significant respiratory distress, and oliguric. She had increased serum lactate (3.9 mmol/l) with normal blood gases, normal renal and liver function tests, and haemoglobin (137 g/l). Antibiotic therapy was broadened and an antifungal was added. Diuretic therapy and milrinone infusion (0.66 mcg/kg/min) were started. After 24 hours, she had more respiratory distress, florid gallop rhythm, persistent tachycardia, and higher lactate. An epinephrine infusion (0.01 mcg/kg/min) was started without clinical improvement. A repeat echocardiogram showed worse ventricular function (left ventricular ejection fraction 13%). A levosimendan infusion at 0.1 mcg/kg/min was started. A loading dose was not given in order to avoid possible hypotension. The infusion was maintained for 70 hours; tachycardia improved significantly (down to 120–130 bpm), systolic blood pressure mildly decreased to 88–95 mmHg, lactate cleared to normal values and epinephrine was discontinued. Echocardiographic follow-up showed improved ventricular function 48 hours into the infusion and persistent improvement at 6 days (left ventricular ejection fraction 59%) (Fig 1a). Milrinone was then discontinued and oral angiotensin-converting-enzyme inhibitor was started. The patient was transferred back to the Haematology-Oncology ward.

Case B

A 4-year-old girl with stage IV neuroblastoma was admitted to the Pediatric Intensive Care Unit for non-invasive positive pressure ventilation and continuous renal replacement therapy for acute renal injury and fluid overload leading to respiratory failure. She had been treated with chemotherapy, adrenalectomy,

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and retroperitoneal dissection, and a recent autologous bone marrow transplant, not yet engrafted. She was on antibiotics and antifungal for febrile neutropenia with negative cultures.

After 36 hours, she developed increasing tachycardia and rising serum lactate without other significant clinical changes. Her blood pressure was higher than normal range (>95th centile); anaemia had been corrected with transfusion. An echocardiogram showed severely reduced left ventricular ejection fraction (20%). A previous echocardiogram 3 weeks earlier was normal. Investigations for cardiomyopathy/myocarditis came back negative for viral infections or reactivations.

A combination of milrinone (0.66 mcg/kg/min) and low-dose epinephrine (0.01 mcg/kg/min) infusions was initiated. Despite this, the heart rate was steadily between 180 and 190, and the serum lactate failed to clear. On repeat echocardiograms, the lowest left ventricular ejection fraction was 12%. Clinically, she was maintaining normal mental status but continued to need non-invasive positive pressure ventilation and continuous renal replacement therapy.

After 48 hours, an infusion of levosimendan was commenced (0.1 mcg/kg/min) for 48 hours. A loading bolus was not given because of the anuric renal failure.

At 12 hours into the infusion, the heart rate was decreasing (160 rather than 180), the blood pressure was between 75 and 95th centile (improved); lactate normalised for the first time in a week. During the next 3 days following the infusion, the patient maintained a normal lactate and a normal heart rate for age. The epinephrine infusion and non-invasive positive pressure ventilation were discontinued and the milrinone infusion was weaned to 0.33 mcg/kg/min. Serial echocardiograms showed an improved left ventricular ejection fraction of 37% over 6 days (Fig 1b). After 4 weeks, carvedilol was started and milrinone discontinued. She was discharged from the unit, although still requiring intermittent haemodialysis. Unfortunately, the patient subsequently died on the ward with intracranial hemorrhage secondary to the rupture of a mycotic aneurysm.

Discussion

We searched the literature (Medline, EMBASE, Pubmed) using the search terms of acute heart failure, levosimendan (limited to 0–18 years of age and reports in English). Namachivayam et al.[6] in a retrospective cohort analysis of 15 children found that levosimendan allowed weaning catecholamines and improved the ejection fraction in those with acute heart failure who survived. Another study with a series of 14 patients with severe heart failure described how a rotating inotropic regimen including dobutamine, milrinone, and levosimendan could lead to an objective clinical improvement and the ability to wean from mechanical ventilation.[7] Braun et al.[8] described a dramatic improvement in the ventricular function of a 12-year-old girl with dilated cardiomyopathy. Similarly, another case report described clinical and echocardiographic improvement after levosimendan infusion in a 14-year-old patient with glycogenosis type Ia who presented with dilated cardiomyopathy and acute heart failure.[9]

We report two cases of the use of levosimendan in children with cancer with acute heart dysfunction and normal to high blood pressure who have not improved on milrinone and low-dose epinephrine infusion.

With levosimendan infusion, both patients showed significant subjective and objective improvement without any notable side effects. In both cases, a loading dose was omitted in order to minimise the risk of hypotension and in the second case also because of renal failure. Nevertheless, haemodynamic improvement was already noticeable at 24 hours and was sustained after discontinuation of the infusion.

Levosimendan was well tolerated despite the requirement for dialysis in one patient, even though renal failure has been described as a relative contraindication.[2,10] Considering the poor prognosis of children with cancer who need intensive care, our report of the observed positive therapeutic effect of levosimendan is significant.

Conclusion

In conclusion, levosimendan can be an effective therapeutic option in acute heart failure, especially in patients who are still maintaining normal or high blood pressure at the expense of tachycardia and increased myocardial oxygen consumption. No side effects were recorded in our experience and it was well tolerated in the patient on continuous renal replacement therapy.

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Conflicts of Interest

None.

Ethical Standards

Verbal and written consents were obtained from patients' parents.

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