Archives de Pédiatrie 25 (2018) 132–135

Available online at ScienceDirect www.sciencedirect.com

Elsevier Masson France EM|consulte www.em-consulte.com/en

Short communication

Hemodynamic support of a 15-year-old waiting for a heart transplant: Is there a role for levosimendan in pediatric heart failure?

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ARTICLE INFO

Article history:
Received 5 July 2017
Accepted 10 December 2017
Available online 1 February 2018

Keywords:
Levosimendan
Heart failure
Pediatrics

ABSTRACT

Decompensated heart failure in children requires rapid and aggressive support. In refractory cases, invasive supportive care is essential to ensure cardiac output. This results in lengthy pediatric intensive care unit (PICU) stays, secondary morbidity, and high cost. Levosimendan may help palliate the pitfalls encountered with the usual treatment. It has been shown to improve hemodynamics and decrease morbidity and mortality from heart failure in adult trials and pediatric cohorts. We report the case of a 15-year-old boy with dilated cardiomyopathy and refractory ventricular dysfunction who was weaned from continuous inotropes and discharged from the PICU with levosimendan while waiting for heart transplantation.

1. Introduction

Pediatric heart failure is a relatively uncommon condition. Eighty-seven percent of children with new-onset heart failure are diagnosed only when they are in severe decompensation and their 5-year survival rate without heart transplantation is less than 50% [1]. Children with decompensated heart failure require immediate and aggressive hemodynamic support with intravenous (IV) inotropes (epinephrine, milrinone, dobutamine), diuretics, and ventilatory support in the pediatric intensive care unit (PICU) [1]. Once the acute decompensation improves, the inotropic agents are weaned and patients are treated with oral medications such as beta-blockers and angiotensin-converting enzyme inhibitor. The hope is for recovery and continued out-of-hospital management. In refractory cases with severe heart failure, oral medication might not be sufficiently effective or even possible. In fact, patients with refractory heart failure can depend on IV inotropes, invasive ventilation, or mechanical heart support to maintain adequate systemic perfusion while waiting for a heart transplant. The usual inotropes are short-acting molecules with a high burden of toxicity that require continuous invasive monitoring in the PICU, as do other cardiac support technologies such as ventricular assist devices (VAD) or extracorporeal membrane oxygenation (ECMO).

Levosimendan, an inodilator, increases cardiac contractility by enhancing troponin's affinity for calcium without modifying the intracellular calcium load and without increasing the myocardial oxygen demand [2–4]. Levosimendan also causes peripheral vasodilation by opening ATP-dependent K+ channels, a molecular target that is thought to provide this drug with cardioprotective and anti-inflammatory properties [2–4]. Levosimendan's unique pharmacokinetic profile and mechanisms of action may help palliate many of the pitfalls encountered with the usual medical management of refractory pediatric heart failure.

We report the case of a 15-year-old boy with dilated cardiomyopathy and associated refractory ventricular dysfunction who was weaned from IV inotropes and successfully discharged from the PICU with levosimendan treatment while waiting for a heart transplant.

2. Case

A 15-year-old boy (57 kg) presented to the emergency department with a history of worsening dyspnea and fatigue for the last month and new-onset chest pain with dizziness and nausea. Blood pressure (BP) was 80/40 mmHg and the child was tachycardiac (125–135 bpm). The first echocardiographic study showed dilated cardiomyopathy with severe ventricular dysfunction and an estimated left ventricular ejection fraction (LVEF) of 17% (Simpson rule). The child was admitted to the cardiology ward, but required transfer to the pediatric intensive care unit (PICU) 24 h later for worsening of his condition (dyspnea, chest pain, and low BP) and echocardiographic studies (LVEF 15%, Simpson rule). Troponin I values were considered normal at the time of admission

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https://doi.org/10.1016/j.arcped.2017.12.003
0929-693X/

and remained normal throughout the hospital stay (admission, 0.06 ng/L; day 7, 0.04 ng/L, and 4 days prior to transplantation, 0.01 ng/L). With diuretics, IV inotropes (epinephrine 0.05 μg/kg/min and milrinone 0.5 μg/mg/min), and noninvasive ventilation (NIV), the child's general condition improved (fatigue, dyspnea, chest pain, BP [98–106/55–65 mmHg]), despite no improvement in LVEF (Simpson rule). After 96 h of continuous inotropes, diuretics, and NIV, the child no longer complained of chest pain, nausea, and fatigue, and was able to eat and stand up. He had frequent transient short and self-resolving episodes of ventricular tachycardia (VT), which were thought to be caused by a combination of the severe state of heart failure and arrhythmogenic beta-stimulating infusion. Epinephrine was tapered off over 24 h with an increase in the milrinone dosage (0.7 μg/kg/min) after a previous unsuccessful wean off epinephrine 24 h earlier; the echocardiographic study showed LVEF at 21% (Simpson rule).

The etiology of the cardiomyopathy was thought to be genetic. Infectious myocarditis was excluded after extensive screening. Cardiac magnetic resonance imaging showed an extremely diminished LVEF and a state of terminal heart failure due to a severely dilated left ventricle cavity. The perfusion study further excluded myocardial inflammation, and therefore myocarditis, all of which were consistent with a late presentation of dilated cardiomyopathy from a probable genetic cause. This diagnosis was later confirmed by intracardiac transplant myocardial biopsy, which showed severely hypertrophic cardiomyocytes with no sign of inflammation and no specific structural anomaly. Considering the very late and severe presentation of this patient, the most probable unfavorable course due to the etiology, the failure to wean IV inotropes and NIV, and the usually long waiting time for organ availability in the pediatric population; the patient was put on the heart transplant waiting list on day 8. On day 11 a minimal dose of captopril (3.125 mg thrice daily) was initiated while weaning milrinone. BP dropped significantly and the child reported dizziness, nausea, and dyspnea. Captopril was stopped on day 12 and epinephrine was restarted to support BP (74/39 mmHg). At this point, the child was dependent on continuous IV epinephrine and NIV in addition to diuretics to maintain cardiac output and experienced frequent VT episodes. The first dose of levosimendan was given on day 15 in the PICU with continuous monitoring of O_2 saturation and heart rate with scope and BP by cuff every 20 min. No bolus was given and the starting dose was 0.05 μg/kg/min with 0.05 μg/kg/min increments every 2 h until a target dose of 0.2 μg/kg/min was reached and then maintained for 24 h. This regimen was based on previously published studies and the product monograph [3–5]. Two hours after the dose of 0.2 μg/kg/min was reached, BP measures were taken every 4 h. Treatment was well tolerated with no episode of hypotension. Epinephrine was weaned off the day after the end of levosimendan infusion as well as NIV 72 h later. The child reported feeling generally better with decreasing frequency and length of VT episodes recorded and his LVEF increased to 24% (Simpson rule). The child was discharged from the PICU to the cardiology ward on day 20. Weekly doses of levosimendan were then scheduled while the child waited for heart transplantation. Every weekly dose was administered under continuous monitoring in the PICU for the duration of the infusion (approx. 24 h) and BP measurements were taken as described above. After the end of each levosimendan infusion, the child returned to the cardiology ward. Heart failure symptoms systematically reappeared the day prior to the weekly dose of levosimendan and resolved in the following 24 h. The patient's favorable general condition permitted initiation of ACEi and beta-blockers in the following weeks (Fig. 1) with the goal of returning home and receiving programmed weekly infusions of levosimendan in the hospital. The trends in the child's NT-pro-BNP and central venous saturation results over time during the hospital stay in relation to the medical treatment received are shown in Fig. 1. The child had a successful heart transplantation on day 53 (LVEF 25% pretransplantation with the Simpson rule), was extubated 9 h following transplantation, and discharged to the ward after 48 h.

3. Discussion

3.1. Mechanism of action

Levosimendan is a calcium-sensitizing pharmacologic agent. It binds to cardiomyocytes troponin C and stabilizes its bond with calcium to help inhibit troponin I, which results in increased muscle contraction force [2,4–6]. This inotropic effect depends on the amount of available calcium in the cytosol [4,5]. Levosimendan does not influence the intracellular storage of calcium, nor does it influence its release or uptake from the sarcomere [4,5]. When the contraction phase is over, calcium is pulled back in the sarcolemma; thus ventricular relaxation is not impaired by the presence of levosimendan [2,4,5]. Calcium-sensitizing agents are the only inotropic molecules that have no impact on intracellular calcium stores and their action is independent of adrenergic receptors. They are therefore less arrhythmogenic and ischemic and less prone to tachyphylaxis than the usual inotropes [4–6]. At therapeutic doses, levosimendan improves myocardial contractility without increasing oxygen consumption and has a positive lusitropic effect (improves diastolic function) [2,4–6].

Levosimendan has vasodilatory properties due to the opening of ATP-dependant K+ channels, which hyperpolarize vascular smooth muscle cells [4–6]. Levosimendan has the ability to vasodilate veins as well as arteries (coronary, pulmonary, and systemic) [2,5]. The opening of these K+ channels at the mitochondrial level, among other molecular targets, is thought to be involved in levosimendan's cardioprotective and antiapoptotic properties in ischemia-reperfusion injury and oxidative stress [3,7]. Other organs could potentially benefit from these protective properties (central nervous system, kidneys, liver, lungs, skeletal muscles) [3,8]. Levosimendan enhances cardiac output by direct inotropic effect, lusitropy, and after-load reduction [5,6].

3.2. Pharmacokinetics

Levosimendan is administered as a continuous infusion of usually 0.2 μg/kg/min for 24 h [5]. Given the associated vasodilation and risk for hypotension, an initial bolus is no longer recommended [9] and the final infusion rate can be reached incrementally depending on the patient's tolerance [5]. Levosimendan has a relatively short half-life (1–2 h) and is N-acetylated in the liver in two metabolites: OR-1855 and OR-1896 [5]. OR-1855 has very little clinically significant activity, whereas OR-1896 has a similar activity to that of levosimendan but with a longer elimination half-life (70–80 h) [4,5]. The peak of action is thought to occur around 48–72 h after the start of the infusion and efficacy can last for 5–10 days [5]. Levosimendan infusions are usually repeated weekly. Renal impairment could prolong duration of action because of decreased OR-1896 clearance [5]. The recommended dosing regimens are extrapolated from adult studies but a prospective pediatric pharmacokinetic trial is currently underway [10].

The amount of OR-1896 in circulation depends on the patient's acetylator status. Slow acetylators (approx. 30% of Caucasians) produce less OR-1896 than rapid acetylators and thus, exhibit 3–3.5 times less total exposure to the active metabolite [4,11]. This could result in the lack of a clinical effect of levosimendan, shorter duration of action, and the need for higher doses.