Case Report

Reversal of Type 2 Pulmonary Hypertension after Levosimendan: A Challenging Approach Bringing New Insights

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Abstract

Among the inotropic agents used in the management of heart failure, levosimendan, in particular, has a selective venodilator property that appears to explain its clinical benefit during pulmonary hypertension (PH). Most of the evidence refers to patients with group 2 PH and consequent right ventricular (RV) dysfunction. In this scenario, the observed benefits may be due to the effect of levosimendan on RV contractility and pulmonary vessel dilation, or to the improvement of left ventricular function and consequent reduction of pulmonary congestion. What we have noticed is that more and more studies are being done on this action and applicability of the drug, appearing in small studies, reviews and formal indications.

Introduction

We know that patients with advanced heart failure with reduced ejection fraction (HFrEF) often have a reduced tolerance to disease-modifying agents, and inotropes are frequently used in emergency and intensive care settings for recovery of organ dysfunction and hemodynamic compensation, as well as in outpatient and palliative settings to improve symptoms and reduce hospitalizations.[1]

Among the inotropic agents, new indications for the use of levosimendan have been discussed, such as its use in patients with pulmonary hypertension (PH). Its action results in an increase in cardiac contractility through sensitization to calcium and promotes vasodilation through the opening of adenosine triphosphate-dependent potassium channels in vascular smooth muscle cells.[1,2]

Case Description

Female patient, 61 years old, with advanced HF of ischemic etiology that began in 2018, history of hospitalization in 2022 for decompensated HFrEF in profile C. She evolved in INTERMACS 3, compensated with dobutamine, euvolemic, and then underwent evaluation for a heart transplant (Tx). Right heart catheterization was performed (Figure 1) with prohibitive values for conventional orthotopic Tx due to fixed PH. The etiology of PH was investigated, angiotomography was negative for pulmonary thromboembolism, and PH group 2 + 3 was assigned due to a previous history of significant smoking and obstructive sleep apnea, confirmed by polysomnography. With no possibility of HeartMate 3 implantation at the time, it was then decided to perform levosimendan to wean off dobutamine and the possibility of hospital discharge for outpatient follow-up with the HF group. Levosimendan was started in a day hospital, 0.05 mcg/kg/min in 30 minutes and then 0.1 mcg/kg/min for 4 hours and repeated every 3 to 4 weeks or as per clinical evaluation, with significant improvement in symptoms, maintaining NYHA II outpatient functional class, using optimized drug treatment and undergoing cardiac rehabilitation. While undergoing treatment, she was hospitalized in November/2023 for evaluation of a ventricular assist device; the patient repeated right catheterization (Figure 2), showing improvement in gradients and pulmonary resistance, showing improvement in pulmonary vascular resistance, being listed for orthotopic heart transplantation on 05/28/24. The patient continues outpatient follow-up, listed and active on the heart transplant waiting list, without prioritization, maintaining intermittent levosimendan infusion when necessary, and cardiac rehabilitation.

Discussion

Although levosimendan is a potentially favorable agent in the treatment of PH and associated pulmonary vascular resistance, there is little data on its use in patients with PH who are contraindicated for cardiac Tx due to prohibitive hemodynamic values due to the risk of RV dysfunction. Marked reductions in pulmonary capillary wedge pressure (PCWP) and improvements in pulmonary circulation have long been recognized as hallmarks of levosimendan during intravenous administration in acute and advanced HF.[3-6] Furthermore, results from preclinical investigations have suggested that levosimendan may reduce right ventricular afterload by relaxing pulmonary arteries and alleviate pulmonary edema by pulmonary venodilation. The safety and efficacy of a repeated weekly intravenous infusion of the levosimendan formulation was tested in a 2021 study in patients with stable PH and HF with preserved ejection fraction, where initial data also implied favorable vascular and clinical responses. Interestingly, reductions in PCWP

Keywords

Pulmonary Hypertension; Heart Failure; Heart Transplantation; Simendan

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Basal state

	Systolic	Diastolic	Mean
Right atrium			8
Pulmonary trunk	90	32	52
Pulmonary capillary			20
Aorta	97	63	72

CI 2,7 *LIminIm²*
TGP: 32
PVR: 8,2 woods

Vasoreactivity test
NPS 1,04mcg/kg/min

	Systolic	Diastolic	Mean
Right atrium			5
Pulmonary trunk	72	22	39
Pulmonary capillary			15
Aorta	90	54	66

CI 2,8 *LIminIm²*
TGP: 24
PVR: 5,8 woods

Figure 1 – *Right Heart Catheterization: 11/01/2022.*

Basal state

	Sistolic	Diastolic	Mean
Right atrium			6
Pulmonary trunk	58	25	36
Pulmonary capillary			23
Aorta	123	73	89

CI 1,83 *LIminIm²*
TGP: 13
PVR: 4,3 woods

Vasoreactivity test
NPS 1,6mcg/kg/min

	Sistolic	Diastolic	Mean
Right atrium			4
Pulmonary trunk	24	12	16
Pulmonary capillary			6
Aorta	101	62	75

CI 2,8 *LIminIm²*
TGP: 19
PVR: 2,17 woods

Figure 2 – *Right Heart Catheterization: 12/06/2023.*

and central venous pressure have been demonstrated in the absence of systemic or pulmonary arterial vasodilation or changes in cardiac index.[7]

In the above report, it is clear that the drug's action falls far short of what is proposed in its routine use: weaning from short-term inotropic drugs and control of symptoms on an outpatient basis. There is a lack of conclusive randomized trials in this field. Several other studies have examined this issue, but with a heterogeneous population, small sample sizes, and inconclusive or even conflicting results.[4]

Conclusion

Reports like this allow us to expand hypotheses, as well as clinical applicability, change perspectives and project new studies. Above all, they allow the possibility of changing the patient's destiny.

Author Contributions

Conception and design of the research; Acquisition of data; Analysis and interpretation of the data and Writing of the manuscript: Betinardi HG; Critical revision of the manuscript for content: Bernardi HGB, Belfort DSP, Biselli B, Chizzola PR, Munhoz RT, Ayub-Ferreira SM, Bocchi EA.

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Ethics approval and consent to participate

This article does not contain any studies with human participants or animals performed by any of the authors.

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