The Uses of Levosimendan in Critically ill Patients

Essay

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List of Abbreviations

ACE	**:**	Angiotensin-converting enzyme
ADHF	**:**	Acute decompensated heart failure
AMI	**:**	Acute myocardial infarction
ARDS	**:**	Acute respiratory distress syndrome
ATP	**:**	Adenosine triphosphate
BELIEF	**:**	The Brazilian Evaluation of Levosimendan Infusion Efficacy
BNP	**:**	Brain natriuretic peptide
CABG	**:**	Coronary artery bypass grafting
cAMP	**:**	Cyclic adenosine monophosphate
CCB	**:**	Calcium channel blockers
cGMP		Cyclic guanisine monophosphate
CI	**:**	Cardiac index
CMK	**:**	Calmodulin-kinase
CN	**:**	Calcineurin
CNS	**:**	Central nervous system
CO	**:**	Cardiac output
COMET	**:**	Center for Overview, Meta analysis, and Evidence-based Medicine Training
COPD	**:**	Chronic obstructive pulmonary disease
COX	**:**	Cyclooxygenase
CPB	**:**	Cardiopulmonary bypass
CPI	**:**	Cardiac power index
CS	**:**	Cardiogenic shock

DHA	**:**	Docosahexaenoic acid
DHF	**:**	Decompensated heart failure
DPD	**:**	Diphosphono-1,2-propanodicarboxylic acid
ECG	**:**	Electrocardiogram
EF	**:**	Ejection fraction
EMA	**:**	European Medicines Agency
EPA	**:**	Eicosapentaenoic acid
ESRD	**:**	End-stage renal disease
FDA	**:**	Food and Drug Administration
FiO2	**:**	Fraction of inspired oxygen
GFR	**:**	Glomerular filtration rate
IABP	**:**	Intra-aortic balloon pump
ICAM-1	**:**	Intercellular Adhesion Molecule 1
ICG-PDR	**:**	Indocyanine green plasma disappearance rate
iNOS	**:**	Inducible NOS
LCOS		low cardiac output syndrome
LevoRep	**:**	Randomised trial investigating the efficacy and safety of pulsed infusions of levosimendan in outpatients with advanced heart failure
LGE	**:**	Late gadolinium enhancement
LIDO	**:**	Levosimendan Infusion versus Dobutamine
LOS	**:**	Length of stay
LPS	**:**	Lipopolysaccharide
LV	**:**	Left ventricle
LVEF	**:**	Left ventricular ejection fraction

MCS	**:**	Mechanical circulatory support
MOF	**:**	Multiorgan failure
NAT2	**:**	N-acetyltransferase
NPs	**:**	Natriuretic peptides
NT-proBNP	**:**	N-terminal pro-BNP
PCWP	**:**	Pulmonary capillary wedge pressure
PET	**:**	Positron emission tomography
PGE2	**:**	Prostaglandin E2
PGF2a	**:**	Prostaglandin F2a
PGI2	**:**	Prostaglandin I2
RAAS	**:**	Renin-angiotensin-aldosterone system
RCT	**:**	Randomized controlled trial
REVIVE I and II	**:**	Randomized Multicenter Evaluation of Intravenous Levosimendan Efficacy trials I and II
RUSSLAN	**:**	Randomized study on Safety and effectiveness of Levosimendan in patients with left ventricular failure due to an Acute myocardial infarct
RV	**:**	Right ventricle
SAH	**:**	Subarachnoid hemorrhage
SBP	**:**	Systolic blood pressure
SPECT	**:**	Single-photon emission computed tomography

SURVIVE	**:**	Survival of Patients with Acute Heart Failure in Need of Intravenous Inotropic Support
SVR	**:**	Systemic vascular resistance
TAPSE	**:**	Tricuspid annular plane systolic excursion
TNF-α	**:**	Tumor necrosis factor alpha
TOE	**:**	Transoesophageal echocardiography
VIP	**:**	Vasoactive intestinal peptide

Introduction

Heart failure is one of the growing problems for both levels of individuals and public health especially as the elderly population is increasing. Acute heart failure is associated with high morbidity and mortality in patients presenting to the emergency department. In the United States, Acute heart failure results in 676,000 annual emergency department visits, with over 80 % of patients requiring hospitalization which is associated with high risk for poor outcomes; more than one-third of patients die or require rehospitalization within 90 days of discharge ***(Go et al., 2014).***

In the treatment of acute decompensation of heart failure caused by left systolic dysfunction, intravenous positive inotropic agents are playing an important role in eliminating hemodynamic abnormalities and improving symptoms ***(Cowie et al., 2000).***

Currently, the most used intravenous positive inotropic agents in clinical practice are β-adrenergic agonists and phosphodiesterase inhibitors. β-adrenergic receptor agonists trigger calcium influx into the myocytes by increasing intracellular cyclic AMP levels through

(cAMP) production, while phosphodiesterase inhibitors increase it by inhibiting its degradation. Increased intracellular calcium levels increase cellular energy needs lead to an increase of myocardial oxygen consumption ***(Slawsky et al., 2000).***

Moreover, it is reported that increased intracellular cyclic AMP and calcium concentration are cardiotoxic. Elevated intracellular calcium concentrations trigger arrhythmias by affecting the electrophysiology of myocytes. As a result, this condition further increases cellular energy need and myocardial oxygen consumption. Although these agents seem useful during the acute exacerbation of heart failure in the short term, it was reported that they cause progression in and increased mortality from the disease ***(Abraham et al., 2005).***

Thus, now, attention is focused on the calcium-sensitizing agents that enhance cardiac performance without increasing intracellular calcium and cAMP levels. Among these groups of agents, levosimendan and pimobendan are known as calcium sensitizers that are available for clinical practice.

Levosimendan is an inodilator developed for intravenous use in hospitalised patients with acutely decompensated heart failure.

Clinical data from heart failure patients show that levosimendan improves haemodynamics without a significant increase in oxygen consumption, reduces symptoms of acute heart failure, has a beneficial effect on neurohormone levels, has a sustained efficacy due to formation of an active metabolite, and suffers no loss of effect in patients under beta-blockade ***(Packer et al., 2013).***

Levosimendan offers a predictable safety profile, no impairment of diastolic function, with no development of tolerance ***(Mebazaa et al., 2007).***

Levosimendan is indicated for the short-term treatment of acutely decompensated severe chronic heart failure in situations where conventional therapy is not sufficient, and in cases where inotropic support is considered appropriate.

In the latest decade, the drug has been tested primarily in the cardiac surgery settings, field in which the drug has shown beneficial hemodynamic and cardioprotective effects and a favorable outcome effect ***(Toller et al., 2013).***

In addition, several studies with repetitive levosimendan dosing in patients suffering from advanced chronic heart failure have shown beneficial effects on haemodynamics, neurohormone levels and symptoms ***(Altenberger et al., 2010).***

Finally, levosimendan has also shown preliminary positive effects - mainly in small-scale studies - in different cardiomyopathies requiring inotropic support ***(Salmenperä et al., 2009).***

Aim of the essay

This essay aims at reviewing the current data, clinical use and the development of levosimendan in the treatment of different critical diseases and its comparison to other inotropes.

Etiology and Pathophysiology of Heart Failure

Definition of the Heart Failure

Heart failure is a clinical syndrome characterized by typical symptoms (e.g. breathlessness, ankle swelling and fatigue) that may be accompanied by signs (e.g. elevated jugular venous pressure, pulmonary crackles and peripheral edema) caused by a structural and/or functional cardiac abnormality, resulting in a reduced cardiac output and/ or elevated intracardiac pressures at rest or during stress ***(P. Ponikowski et al., 2016).***

Terminology

- **Terminology related to the ejection fraction (EF)**

1- Heart failure with reduced EF: <40%.

2- Heart failure with midrange EF: 40 -49%.

3- Heart failure with preserved EF: >49% ***(Nadruz et al., 2017).***

- **Terminology related to the course of heart failure**

1- Asymptomatic LV systolic dysfunction: A patient who has never exhibited the picture of HF with a reduced LVEF.

2- Chronic HF: Patients who have had HF for some time.

3- Stable: A treated patient that have remained unchanged symptoms for at least 1 month.

4- Decompensated: If chronic stable HF deteriorates ***(Kalter-Leibovici et al., 2017).***

5- New-onset (de novo) HF may present acutely or subacute (gradual) fashion.

6- Congestive HF: Acute or chronic HF with evidence of volume overload.

7- Advanced HF: Severe symptoms, recurrent decompensation and severe cardiac dysfunction (***Ural et al., 2016)***

- **Terminology related to the severity of heart failure**

The NYHA functional classification:

Stage I: No limitation of physical activity.

Stage II: Dyspnea with ordinary physical activity.

Stage III: Dyspnea with less than ordinary physical activity.

Stage IV: Symptoms of heart failure at rest ***(P. Ponikowski et al., 2016)***

Etiology of Heart Failure:

- **Diseased Myocardium**

1- Ischemic heart disease

2- Toxic damage (substance abuse, heavy metals, cytostatic drugs, immunomodulating drugs, antidepressant drugs, antiarrhythmics and radiation).

3- Immune-mediated and inflammatory damage.

- Related to infection as Bacteria, spirochetes, fungi, protozoa, parasites (Chagas disease).
- Not related to infection as Lymphocytic/giant cell myocarditis, autoimmune diseases, hypersensitivity and eosinophilic myocarditis (Churg–Strauss).

4- Infiltration.

- Related to malignancy (Direct infiltrations and metastases).
- Not related to malignancy (Amyloidosis, sarcoidosis, haemochromatosis (iron), glycogen storage diseases (e.g. Pompe disease), and lysosomal storage diseases (e.g. Fabry disease).