

## Use of levosimendan in the ICU



Levosimendan is an inodilator that promotes cardiac contractility primarily through calcium sensitisation of cardiac troponin C and vasodilatation via opening of adenosine triphosphate-sensitive potassium (KATP) channels in vascular smooth muscle cells. The drug also exerts organ-protective effects through a similar effect on mitochondrial KATP channels.

Levosimendan has been demonstrated to have potential utility in a wide range of critical illness situations encountered in intensive care unit (ICU) medicine: haemodynamic support in cardiogenic or septic shock; weaning from mechanical ventilation or from extracorporeal membrane oxygenation; and in the context of cardiorenal syndrome.

A review paper, authored by experts from nine European countries (Austria, Belgium, Czech Republic, Finland, France, Germany, Italy, Sweden, and Switzerland), examines the clinical and experimental data for levosimendan in these situations and concludes that, in most instances, the evidence is encouraging, which is not the case with other cardioactive and vasoactive drugs routinely used in the ICU.

"It must be acknowledged, however, that in each sphere of application, the evidence is incomplete or indicative rather than conclusive, and further clinical evaluation will be needed to substantiate the case for levosimendan and to refine the patient categories and dosage schedules likely to be associated with the greatest clinical benefit," according to the authors.

### Haemodynamic support in critical care

Levosimendan has been studied in several therapeutic applications, particularly in the management of acute heart failure (AHF) patients with low cardiac output and in high-risk cardiac surgery. The drug has also shown preliminary positive effects in a range of other conditions requiring inotropic support, including right ventricular failure, cardiogenic shock (CS), septic shock, and Takotsubo cardiomyopathy.

Acute myocardial infarction (AMI) is the most common etiology of CS but CS may arise from any situation of acute, severe dysfunction in either ventricle of the heart. The standard of care in CS consists of primary percutaneous coronary intervention for AMI, fluid therapy, vasopressors, inotropes and, in the last resort, mechanical assistance. Data from initial comparator studies indicate that levosimendan may be a useful addition to this regimen.

The currently available clinical evidence in septic shock indicates that: (1) Levosimendan can successfully replace dobutamine in supporting severe de novo AHF due to septic cardiomyopathy (SCM), with additional positive extracardiac effects owing to amelioration of multiple-organ failure (MOF); and (2) Indiscriminate use of levosimendan (i.e., without selecting severe cases of cardiovascular failure) to prevent the development of MOF is safe from a haemodynamic perspective but may confer no clinical benefit.

### Weaning from the ventilator

About 10%–20% of intubated patients in ICUs are difficult to wean from mechanical ventilation, resulting in increased morbidity and mortality. The pathophysiology of muscle weakness in these patients is complex but includes muscle fibre atrophy and reduced calcium sensitivity of the contractile proteins. Because respiratory muscle troponin resembles cardiac troponin, it is plausible that levosimendan may enhance muscular contractility in the same way that it enhances cardiac contractility. This supposition has support from in vitro data, experimental research, and a healthy volunteer study. Positive effects were seen in both slow and rapid diaphragm muscle fibres.

### Weaning from extracorporeal membrane oxygenation

Most patients require inotropic drugs to support myocardial contractile function during weaning from venoarterial extracorporeal membrane oxygenation (VA-ECMO), and the limited clinical evidence currently available suggests that levosimendan offers some important advantages over other inotropes for this vulnerable period: no increase in myocardial oxygen consumption, a prolonged cardiovascular effect (days), and improvement in endothelial function.

## Other settings

It should be noted that the HFA-ESC Task Force on Takotsubo syndrome advocates levosimendan as the single form of inotropic support in cases of unavailable extracorporeal life support (ECLS). Case reports are encouraging, and the pathophysiology is conceptually a good fit to the properties of levosimendan.

The authors cite that some clinical trials on the efficacy and safety of levosimendan in AHF showed a significant improvement in survival, whereas some (the larger ones) did not, but the bulk of evidence did overall support the efficacy and safety of the drug. Based on these findings, a market authorisation was granted in over 60 countries, with the notable exception of the U.S. and the UK.

"Central to future investigations must be the identification of robust and relevant end points. An improvement in survival/mortality may be plausible in cases where levosimendan substitutes for an adrenergic inotrope with a documented propensity to increase mortality. In other settings, however, it is not obvious that a mortality gain can be assumed nor is it certain that any such gain, welcome as it would be, would be the most pertinent measurement of any treatment effect," the authors write.

Source: [Journal of Cardiovascular Pharmacology](#)

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Published on : Thu, 10 Jan 2019