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Levosimendan and organic protection

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Introduction

The use of levosimendan has not only improved the outlook of patients with pump failure, limiting itself to be a good inotropic: it also had as results the extension of its use to the organ protection realm. Numerous articles have been published of levosimendan (the (-) enantiomer of {(4- (1,4,5,6-tetrahydro-4-methyl-6-oxo-3pyridazinyl) phenyl) hydrazono} propanedinitrile), referring to its molecular mechanisms of action and its effects. We have reviewed them in order to clarify ideas and give some general recommendations.

Pharmacokinetics

Levosimendan is an inotrope and also a vasodilator, and its two fundamental mechanisms of action are the calcium sensitizing effect and its effect on ATP-sensitive potassium channels. We may add to this the phosphodiesterase inhibition, the effects on biomarker and the effects on energy balance [1-3]. Taking all these mechanisms together, as explained below, helps understand its organ-protective character.

Before starting the study of levosimendan we need to understand its long duration, despite its 1 to 1.5 hours term average living. About a 5% of the drug is converted to the metabolite OR-1855 in the large intestine, and then acetylated in the liver to form the active metabolite OR-1896. This metabolite binds to plasma proteins by 40% compared to levosimendan which binds up to 98%, which explains why a relatively low total plasma level of the metabolite may evoke clinically significant effects [4]. Moreover this active metabolite has an about 75 to 80 h elimination life term, allowing cardiovascuar effects to persist up to 7 to 9 days after discontinuation of a 24-hour infusion of levosimendan [5,6]. Renal dysfunction has little effect on the drug's final plasma concentration but appears to prolong the elimination term of OR-1896. Liver cirrhosis slightly prolongs the elimination term of levosimendan, although its effect on the metabolism of OR-1896 is unknown [7,8].

Calcium sensitization and lusitropy

The basis of Ca sensitizing mechanism is the interaction with the Ca saturated cardiac troponin C , in a hydrophobic region of its N-domain near the so-called D/E linker region [9-11]. Troponins are heterotrimeric complexes consisting of a troponin T (TnT) anchoring the complex by binding to tropomyosin, a troponin C (TnC), whose function is to bind to calcium and troponin I (TnI), which is the inhibitory unit. Muscle contraction begins by calcium binding to the TnC altering interaction between TnC and TnI. This causes the inhibitory region of TnI to detach from acting and bind to TnC [12]. Levosimendan stabilizes Ca saturated TnC, allowing a prolonged interaction between TnC and TnI, thereby promoting contractile force without an increase in the amplitude of intracellular Ca transient [9,10], and without inhibiting ventricular relaxation [13]. An increase in calcium sensitivity should lead to negative lusitropy, but levosimendan does not prolong relaxation time [14]. On the contrary, in patients with left ventricular hypertrophy it exerts a direct positive lusitropic effect as it shortens isovolumic relaxation time and improves left ventricular filling [15-17].

Phosphodiesterase inhibition

Both levosimendan and OR-1896 are highly selective inhibitors of the phosphodiesterase (PDE) III isoform. Some studies have tried to relate the lusitropic and inotropic effect of levosimendan with cAMP signaling pathway [18,19]. However, for a detectable increase in the level of cAMP and consequently intracellular calcium, inhibition of at least two isoforms of PDE is required, preferably PDE III and PDE IV [20,21], and it is clearly demonstrated that nor levosimendan neither its active metabolite affect the function of other PDE isozymes at their therapeutic concentrations [22]. Levosimendan this way, unlike other inotropes, is highly selective for PDE III, and thus allows other intracellular PDE catabolism cAMP to its physiological levels [23]. Higher than therapeutic doses or different species dependent cyclic nucleotide signaling, could explain the results of the above studies, since results of several investigations indicate that alteration in intracellular Ca concentration (resulting from cAMP elevation secondary to PDE inhibition) are not a prerequisite for the cardiac effects of levosimendan [24-26].

Potassium channels and vasodilatation

Levosimendan- and OR-1896- mediated vasodilatation have been linked in numerous studies to action on different potassium channels in arterial myocytes. This action has involved the opening of these channels, with the consequent outflow of potassium and hyperpolarization of the cell. Different potassium channels have been linked (glibenclamide- sensitive K^+ channel, voltage-gated K^+ channels, Ca^{2+}-activated K^+ channels and ATP-sensitive K^+ channels) and the proportion thereof depends on the type of blood vessel and also on vascular diameter. Vasodilatation has been demonstrated at the arterial sides of the pulmonary, coronary and peripheral circulations and at the venous sides of the portal and saphenous systems [27- 33]. Endothelial mechanisms also have been implicated in vasodilatation with nitric oxide production secondary to the use of levosimendan [34].

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Mitochondrial ATP-sensitive potassium channels and energy balance

The cardiac muscle has high energy demand, primarily used for excitation and contraction coupling and force generation. It is necessary, therefore, a proper fit between the production of ATP and the workload without which energy resources quickly drain [35]. We need to know how the heart muscle makes this link and here is where potassium channels, acting as metabolic sensors, seem to play an important role [36-39]. We find this kind of potassium channel formed as heteromultimers of inwardly-rectifying potassium K+ channel (Kir) 6.2 and ATP-Binding Cassette (ABC) Sulfonylurea Receptor (SUR) 2A proteins [40,41]. The domain SUR will translate local levels of ADP and ATP, which will depend on ATPases and phosphotransfer reactions, to channel function. In cells where metabolites mobility is limited between their microdomains, reactions of these enzymes acting on potassium channels will translate internal nucleotide levels into changes in membrane excitability, thus achieving a coupling between demand and metabolic reserves [42-44]. The domain SUR through its structure will bind to ATP, having ability to hydrolyze it and convert to ADP, and also will be attached to the Kir domains. When bound to ATP, it translates the potassium channel closure, and when it is already attached to posthydrolytic ADP it translates the channel opening. In situations of stress, we found high levels of ADP, prevailing therefore open channel shape [45]. Thus, in situations of high energy demand the opening of potassium channels adjust the membrane excitability and produces a shortening of the action potential duration, limiting intracellular calcium loading. This will ensure electrical stability and diastolic interval prolongation, getting a suitable differential intracellular calcium concentration between systole and diastole, which is optimal for cardiac relaxation [37,38,42]. All this helps us to see how the levosimendan, acting on these receptors, plays a fundamental role in the regulation of energy metabolism, preventing calcium overload of mitochondria and thereby preserving the high-energy phosphates and regulation of mitochondrial volume [46,47]. A recent study about the effects of levosimendan on mitochondria in septic shock concludes that it protects the mitochondria of oxidative stress and may thus mitigate the bioenergetic failure, reinforcing the idea of protecting the energy metabolism through action on the ATP-sensitive potassium channels [48].

Biomarkers

As biomarkers we refer to a series of biological substances that act as markers of stress and myocytes damage. These substances are believed to be related to the pathogenesis and progression of chronic heart failure [1].The elevation of Brain Natriuretic Peptide (BNP) in heart failure has been shown to have a direct relationship with mortality, and levosimendan causes a significant drop in its plasma levels [49,50]. Further still, the greater falling in BNP with the treatment has a better prognosis at six months in the patients who got it [51]. Besides decreasing the BNP, levosimendan gets reduction of other neurohormonal markers such as IL-6 and CRP, both proinflammatory cytokines, and nuclear factor kappa B (NF-KB), another cytokine which is released in situations of hypoperfusion and has arrithmogenic properties [52,53]. All this suggests an immunomodulatory effect of levosimendan, improving the neurohormonal and inflammatory situation and implicating a potential interference with cardiomyocyte apoptosis and myocardial remodeling, supplementing its vasodilators and inotropic effects [1].

Mechanism of action

Levosimendan increases the contractile force of the cardiac muscle fibers; causes coronary, arterial and venous vasodilatation and exerts an organprotective effect against ischemia [1].

Brain protection

Cerebral ischemia activates cellular processes, including apoptosis, inflammation, inhibition of protein synthesis and increased oxidative stress, which persist despite the restoration of substrate delivery [54]. Every minute of lost cerebral perfusion in the human brain results in a loss of neurons that is equivalent to the loss of neurons after 3.6 years of the normal human ageing process [55].

The only valid form of therapy to improve neurological outcome is to perform therapeutic hypothermia 12 to 24 h following resuscitation [56]. Concomitant with the symptomatic therapy used to achieve return of spontaneous circulation, therapeutic options employed to minimize the reperfusion injury have to be considered [57].

Levosimendan has been shown to be neuroprotective in the spinal cord when applied prior to or during ischemia.

Evidence of levosimendan'sneuroprotective properties include reduced cell death, inflammatory response and lipid peroxidation; besides, improved function after transient ischemia [58,59].

The important role of the mitochondrial ATP dependent potassium channels in cerebral ischaemia-reperfusion injury and positive action of other activators (diazoxide) on neuronal injury create hopes for neuroprotective effects of this drug [60,61].

Kidney protection

Renal dysfunction is common in patients with heart failure [62] and other clinical settings in which cardiac function is commited [63,64]. Due to the complex interactions underlying this cardiorenal syndrome, kidneys can be affected both in the short and long terms [65]. Impaired renal function has impact on the prognosis of patients with compromised heart function [66]. In advanced chronic heart failure, renal impairment was a stronger predictor of mortality than left ventricular ejection fraction or New York Heart Association class [67].

Anti-oxydant and anti-apoptotic effects of levosimendan could be related to protection against renal ischemic reperfusion injury and improvement of renal function in heart failure cases [65]. Treatment with this drug may reverse the on-going processes of renal dysfunction through protective mechanisms involving macro or microcirculation. Renal blood flow depends on renal vascular resistance and arterial and venous pressures. Central venous pressure is an important independent predictor of glomerular filtration rate in patients with heart failure [68].

Levosimendan provides functional improvement of the right ventricle and significant reductions in right-sided pressures, including central venous and pulmonary artery wedge pressures. This alleviates the increased renal vein pressure that may impair renal function through a decreased perfusion pressure and a decrease in glomerular filtration rate [69-71].

This drug induces a preglomerular vasodilatation (increases renal blood flow and glomerular filtrate rate), suggesting that the beneficial renal effects of levosimendan in patients with heart failure and impaired renal function may not only be caused by an increase in cardiac output, but also by a specific renal vasodilator action [72]. ATP

sensitive potassium channels are also present in afferent arterioles and may play a role in the effects of this drug on renal blood flow [73].

In relation to the microcirculation, levosimendan may augment renal perfusion via vasodilatation arising from its ATP sensitive potassium channel agonism. Additionally, it may reverse angiotensin-2 mediated mesangial cell contraction [74], thereby increasing glomerular capillary surface area [75].

Liver and intestine protection

Levosimendan increases blood flow in intestine and liver, reducing resistance in these organs. Its effects on the oxygenation of the microvasculature of gastric mucosa are higher than others drugs (dobutamine and milrinone); so we must use it to improve the oxygenation of gastrointestinal mucosa in case with a high risk of splanchnic ischemia [53].

Cardio protection

The cardioprotective effect has a multifactorial cause:

1. The reduction in preload and afterload improves cardiac work. Levosimendan improves the contractile force during systole without negatively affecting the relaxation during diastole. This leads to higher cardiac contractility without increasing oxygen consumption by the myocardium [2,15].

2. The increase in coronary blood flow improves the perfusion of cardiac cells [76].

Levosimendan protects against ischemic events, is able to reduce the size of the infarcted area and improves cardiac function recovery after global ischemia [77]. For this reason levosimendan pretreatment has been suggested for the prevention of ischemia-reperfusion injury in coronary bypass surgery, [78] because myocardial contractility, stroke volume and cardiac output are preserved in spite of the hypoxic insult [79].

Recent studies show its low arrhythmogenic profile because it acts against inflammation and oxidative damage, which are involved in the pathogenesis of arrhythmias [80,81].

Furthermore, it acts against myocardial stunning both ischemic disease and sepsis [82]. Levosimendan improves systemic hemodynamic and regional perfusion in patients with septic cardiac dysfunction [83]. Its inotropic properties are not compromised in the acidotic or hypoxic heart [84]. Acute respiratory distress syndrome is frequently associated with increased pulmonary vascular resistance and systolic load of the right ventricle, which is associated with high morbidity and mortality [85]. Levosimendan, with potential pulmonary vasodilator properties, improves right ventricle performance [86].

Patients undergoing cardiac surgery with a reduced ejection fraction and who received levosimendan before, during, or after surgery presented lower mortality and myocardial injury than other patients. Furthermore, it was reduced the development of postoperative low output syndrome as well as the need for inotropic and vasoactive agents and intra-aortic balloon counter pulsation [87].

The administration of levosimendan facilitates disconnection from CPB thanks to its inotropic and lusitropic effects and reduces the need for mechanical support due to weaning failure and the ICU stay. Markers of tissue oxygenation and myocardial damage (lactate and troponin T) are lower with this drug [88,89].

Levosimendan decreases levels of brain natriuretic peptide. The magnitude of the reduction in brain natriuretic peptide levels caused by levosimendan treatment is correlated with improved clinical outcomes at six month. Brain natriuretic peptide levels can be regarded as a prognostic factor of its effectiveness [90].

Levosimendan alters levels of cardiac biomarkers related to the progression of congestive heart failure; it reduces proinflammatory cytokines, has a favorable effect on markers of oxidative stress and prevents myocardial apoptosis in myocytes [91].

Conclusions

Levosimendan is an inotropic agent with vasodilator effects, thanks to a triple mechanism of action: sensitizing effect of calcium channels in cardiac myofilaments fibers, opening of ATP-sensitive potassium channels in smooth muscle cells and opening the ATP-sensitive potassium channels in cardiac cells mitochondria. Through this triple mechanism levosimendan increases the contractile force of cardiac muscle fibers, causes both arterial and venous peripheral vasodilation and has a cardioprotective effect against ischemic situations [92].

The increase in the flow of potassium associated with the opening of ATP-sensitive channels of mitochondria seems sufficient to protect and preserve mitochondrial function, mainly through standardizing matrix and the intermembrane space volume under stress as ischemia or reperfusion injury [93,94]. It has recently been published a meta-analysis of 14 clinical trials of patients selected for cardiac surgery in which levosimendan was used. Its authors found a significant reduction in mortality in patients having a decreased dejection fraction of the left ventricle.

It were also found decreased postoperative complications in patients to whom the drug was given. There is no evidence however of decreased mortality in patients who develop low cardiac output regardless of previous situation and the mechanism by which this decrease would happen. The reason why levosimendan improves outcomes in cardiac surgery may be related to its ability to improve contractility without increasing oxygen consumption and its ability to recover stunned myocardium. These hemodynamic effects are much greater than with dobutamine and unlike this it is not affected by concomitant use of beta-blockers, as the effect of levosimendan is not dependent on beta-adrenergic receptors. Improvement of stunned myocardium by the rest of catecholamines is based on an increase in intracellular calcium in the myocytes, which in turn leads to an increase in the possibility of arrhythmia and impaired myocardial relaxation. Unlike levosimendan, mechanism has been proposed as part of the apoptosis [95,96]. Besides cardioprotection against ischemic events and stunning effect protection levosimendan may have effects against ischemia in other organs. Neurological complications in the immediate postoperative period of cardiac surgery are a major cause of morbidity and mortality, causing an increase in the use of health resources and leading to functional limitations in those who survive.

In these tables cardiac dysfunction is one of the most important predisposing factors. Recently cognitive impairment has been identified in 83% of patients undergoing cardiac surgery [97]. At brain level in vitro studies levosimendan has shown its possible neuronal protection during ischemic situations or neuronal hypoperfusion, being able to decrease motor dysfunction due to created spinal cord ischemia [98]. Acute Renal Failure (ARF) is a common complication of cardiovascular surgery, with a reported varying incidence which depends on both the used FRA definition and the studied population, but in most estimates

close to 30%, reaching values at mortality series between 70% and 90% [99,100]. There have been several studies on the possible beneficial effect of levosimendan on renal function in postoperative cardiac surgery, noting that of Bragadottir *et al.*, in which an improvement in glomerular filtration rate, renal blood flow and renal oxygenation is observed regardless of the improvement in cardiac function [101]. A recent meta-analysis demonstrated that perioperative administration of levosimendan has beneficial effects at the level of renal function, although the heterogeneity of the studies makes interpretation difficult [30].

We have recently published two articles and an editorial regarding the use of levosimendan in cardiac surgery, showing the cardiac benefit of its administration in patients with ventricular dysfunction and its possible organ protection properties [53,85].New jobs are needed for the evaluation of the promising organ protection role of levosimendan, an inodilator which becomes a perioperative drug having multiorgan conditioning properties.

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