European Journal of Pharmacology 740 (2014) 596–602

Contents lists available at ScienceDirect

European Journal of Pharmacology

journal homepage: www.elsevier.com/locate/ejphar

Review

The role of Levosimendan in cardiopulmonary resuscitation

Giolanda Varvarousi [a], Antonia Stefaniotou [a], Dimitrios Varvaroussis [a], Filippia Aroni [a], Theodoros Xanthos [a,b,*]

[a] National and Kapodistrian University of Athens, Medical School, MSc Cardiopulmonary Resuscitation, 75 Mikras Asias Street, 11527 Athens, Greece
[b] Hellenic Society of Cardiopulmonary Resuscitation, Athens, Greece

ARTICLE INFO

Article history:
Received 5 April 2014
Received in revised form
13 June 2014
Accepted 17 June 2014
Available online 24 June 2014

Keywords:
Epinephrine
Cardiopulmonary resuscitation
Levosimendan
Cardioprotective
Neurological outcome

ABSTRACT

Although initial resuscitation from cardiac arrest (CA) has increased over the past years, long term survival rates remain dismal. Epinephrine is the vasopressor of choice in the treatment of CA. However, its efficacy has been questioned, as it has no apparent benefits for long-term survival or favorable neurologic outcome. Levosimendan is an inodilator with cardioprotective and neuroprotective effects. Several studies suggest that it is associated with increased rates of return of spontaneous circulation as well as improved post-resuscitation myocardial function and neurological outcome. The purpose of this article is to review the properties of Levosimendan during cardiopulmonary resuscitation (CPR) and also to summarize existing evidence regarding the use of Levosimendan in the treatment of CA.

Contents

1. Introduction

Although the rates of initial resuscitation from cardiac arrest (CA) have increased over the past years, long term survival rates remain dismal (Berdowski et al., 2010). Epinephrine is the vasopressor of choice in the treatment of CA because it increases coronary perfusion pressure (CPP) and thus return of spontaneous circulation (ROSC) (Callaway, 2013). However, the efficacy of epinephrine in the setting of CA has been questioned because it has no apparent benefits for long-term survival or neurologic outcome (Xanthos et al., 2011). Moreover, modern management of CA should aim at improving not only ROSC rates but also long-term survival.

Levosimendan is a unique inodilator (Endoh, 2001), with cardioprotective and neuroprotective effects (Nieminen et al., 2013). Levosimendan is the treatment of choice in acute and decompensated chronic heart failure states (Berger et al., 2007). Moreover, Levosimendan may be particularly beneficial in the treatment of post-operative myocardial dysfunction following cardiac surgery (De Hert et al., 2007), right ventricular failure (Poelzl et al., 2008) and sepsis (Zager et al., 2006). Several studies suggest that the administration of Levosimendan during cardiopulmonary resuscitation (CPR) and the post-resuscitation phase is associated with increased rates of ROSC (Koudouna et al., 2007), as well as improved post-resuscitation myocardial function (Huang et al., 2005a) and

* Corresponding author at: National and Kapodistrian University of Athens, Medical School, MSc Cardiopulmonary Resuscitation, 75 Mikras Asias Street, 11527 Athens, Greece. Tel.: +30 2110121756.
E-mail address: theodorosxanthos@yahoo.com (T. Xanthos).

http://dx.doi.org/10.1016/j.ejphar.2014.06.024
0014-2999/

neurological outcome (Kelm et al., 2014). Although the use of Levosimendan has not been implemented in the latest guidelines on resuscitation (Nolan et al., 2010), its pharmacological actions make it a promising agent in the treatment of CPR.

The purpose of this article is to review the properties of Levosimendan during CPR and also to summarize existing evidence regarding its use in the management of CA.

2. Levosimendan's actions

Levosimendan is a non-adrenergic inotropic calcium sensitizer (Endoh, 2001) that exerts its inotropic effect principally via binding to the Ca^{2+} saturated troponin C of the myocardial thin filament (Jamali et al., 1997). Its ability to enhance calcium responsiveness of the myofilaments potentiates cross-bridge formation, thereby augmenting contractility and enhancing relaxation (Haikala et al., 1995; Janssen et al., 2000). Moreover, it has anti-stunning effects and reduces post-resuscitation myocardial dysfunction (Figgitt et al., 2001).

Levosimendan has also vasodilatory and anti-ischemic effects mediated by the opening of ATP-sensitive potassium (K_{ATP}) channels in the sarcolemmal membrane of vascular smooth muscle cells (Kaheinen et al., 2001). It induces vasodilation in systemic circulation (De Witt et al., 2002; Slawsky et al., 2000) and lowers both preload and afterload, improving tissue perfusion. It also exerts some vasodilator effects on the coronary (Michaels et al., 2005) and cerebral circulation (Kelm et al., 2014). By the opening of mitochondrial K_{ATP} channels in cardiomyocytes, it exerts pleiotropic effects and appears to be improving long-term benefit in CA (Nieminen et al., 2013). Levosimendan has pre-conditioning and anti-apoptotic properties (Kersten et al., 2000), which protect mitochondria from ischemia–reperfusion (I/R) injury. Moreover, it exerts some anti-inflammatory effects (Parissis et al., 2004) (Fig. 1).

However, the use of Levosimendan may as well have adverse effects. Its use has been associated with both hypotension and hypokalemia (Mebazaa et al., 2007), and its use has been associated with increased frequency of both atrial fibrillation and ventricular tachycardia (Moiseyev et al., 2002). It is known that Levosimendan has the ability to inhibit phosphodiesterase III and open K_{ATP} channels, which might provoke arrhythmogenesis (Gruhn et al., 1998). Inhibition of phospodiesterase III increases calcium entry into the myocardial cell and enhances atrioventricular conduction (Arnold, 1993). Moreover, the activation of K_{ATP} channels during myocardial ischemia increases potassium efflux and may lead to action potential shortening and depolarization of the resting membrane. The above electrophysiological changes may facilitate the development of tachyarrhythmias (Hatcher et al., 2011).

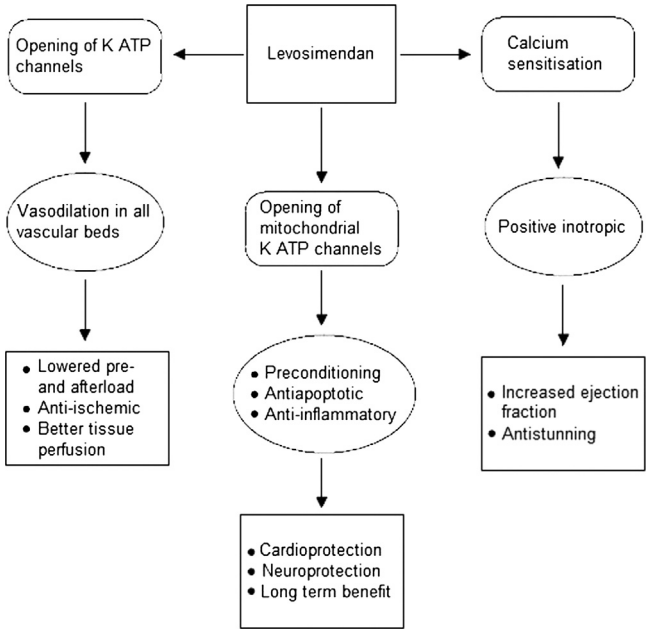

Fig. 1. Beneficial effects of levosimendan during cardiopulmonary resuscitation.

3. Effects of Levosimendan during cardiopulmonary resuscitation

CPP, defined as the difference between the aortic pressure and the pressure in the right atrium at the onset of diastole (Paradis et al., 1990), is known to be a prognostic factor for ROSC and survival in the setting of CPR (Frenneaux, 2003). Although epinephrine induces vasoconstriction and increases CPP (Xanthos et al., 2011), it exposes the myocardium to a vigorous increase in oxygen demand through its beta adrenergic effect. Epinephrine triggers calcium influx into the myocytes by increasing intracellular cAMP levels. The increased cytosolic Ca^{2+} increases myocardial oxygen consumption (Ornato, 1993; Slawsky et al., 2000) and results in critically decreased endocardial blood flow as well as in ischemic injury.

In contrast to classic inotropic agents, Levosimendan elevates the oxygen availability to the myocardium during CPR, reducing the pressure of the right atrium due to its peripheral vasodilatory effect (Tavares et al., 2008), which leads to higher CPP. The blood supply to the myocardium is therefore enhanced at a time when oxygen requirements are increased (Gregorini et al., 1999). The enhanced myocardial contractility produced by Levosimendan (Endoh, 2002) along with the higher CPP allows the maintenance of an adequate cardiac output during resuscitation. Furthermore, Levosimendan has a direct vasodilator effect on coronary arteries (Gruhn et al., 1998) and enhances coronary blood flow (Kivikko and Lehtonen, 2005). In this way it counteracts intramyocardial coronary arteriolar vasoconstriction induced by the alpha-1 adrenergic action of epinephrine. Koudouna et al. conducted an animal study in order to test whether the addition of Levosimendan to epinephrine would result in an increased CPP. Ventricular fibrillation was induced in 20 piglets and left untreated for 8 min. The animals were randomized to receive Levosimendan (0.012 mg/kg) or placebo combined with epinephrine (0.02 mg/kg) at the beginning of CPR. The CPP was significantly higher during CPR in the group of animals that received Levosimendan and epinephrine ($P < 0.05$). Furthermore, initial resuscitation success was improved when epinephrine was combined with Levosimendan instead of placebo in the pigs (Koudouna et al., 2007) (Table 1).

Prolonged CA is accompanied with global hypoxia and severe acidosis that depresses myocardial function by impairing the responsiveness of myofilaments to Ca^{2+} (Than et al., 1994; Wayne et al., 2002). Although catecholamines remain the mainstay of treatment in the setting of prolonged CA, studies have shown that acidosis limits their effectiveness to reverse acidosis -induced myocardial contractile impairment (Hindman, 1990; Wayne et al., 2002). Prolonged CA leads to beta-adrenergic receptor down-regulation (Modest and Butterworth, 1995), reduction of formation of cAMP (Tanaka et al., 1998) and inhibition of Ca^{2+} exchange. Catecholamine resistant CA lead to the false need for multiple repetitive doses of epinephrine (Achleitner et al., 2000; Wenzel et al., 1999), which is an independent predictor of poor neurologic outcome (Behringer et al., 1998).