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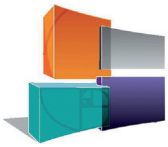

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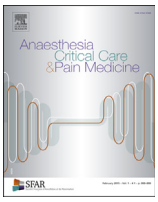

Editorial

Should we keep levosimendan in our pharmacies? Yes, undoubtedly!

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In contradiction to previous reports, the meta-analysis by Zhu et al. published in this issue of ACCPM suggests that prophylactic administration of levosimendan does not improve 30-day mortality among patients with altered left ventricular function undergoing cardiac surgery [1]. This finding combined with the negative results of the three large randomised controlled trials on levosimendan published in 2017 [2–4] could easily be used as an additional "piece of evidence" to support the idea of removing from our shelves a drug that has no clear evidence to support its usefulness. Such an expedited decision would certainly be a big mistake and lead to discard another potentially helpful molecule from our armamentarium.

Indeed, treating patients with decompensated heart failure is sometimes a challenge and being able to have a variety of drugs to manipulate the cardiovascular system is crucial. The classical inotropic agents all result in an increase in free cytosolic calcium, which in turn increases the contraction strength at the expense of a rise in myocardial oxygen consumption generated by the sarcoplasmic reticulum uptake of this ion during diastole. This side effect is clearly unwanted in patients with end-stage heart failure for whom oxygen delivery is limited. The tendency to increase mortality observed with beta adrenergic agents [5,6] or phosphodiesterase inhibitors [7] might be related, in part, to the worsening in myocardial energetic imbalance. In this regard, levosimendan offers a unique reinforcement in myocardial contractility by increasing the affinity of troponin C for calcium, resulting in prolonged actin-myosin cross-bridges and increased contractile force, without the burden of increased intra-cellular calcium concentration and, therefore, no increase in myocardial oxygen consumption. This property is undoubtedly very attractive, especially for patients with ischaemic heart disease. Levosimendan is also an ATP-dependent potassium channel opener at the level of the vascular smooth muscle and in the cardiac mitochondria. The resulting vascular effect is a potent vasodilatation that will therefore facilitate left ventricular ejection by reducing afterload. The cardiac mitochondrial effect is credited for conferring a cardiac protection through pre- and post-conditioning as well as anti-stunning effects. The large randomised controlled trials published so far failed to show an improvement in mortality with levosimendan, but at least there was no worsening in prognosis with respect to placebo. On the other hand, evidence accumulates to suggest that beta-agonists are associated with increased mortality [8].

There are several reasons why it would be unwise to eliminate levosimendan based on the recent negative results and their meta-analysis. The most obvious of them is that all patients with chronic heart failure who are not contraindicated for beta-blockers receive these drugs as a first-line therapy according to current guidelines [9]. However, acute decompensation may occur and beta-blockade is likely to impair the response to beta-agonists agents. In such patients, being able to provide an inotrope that will not be antagonised is of paramount importance. Another remarkable feature of levosimendan, that differentiates it from classic beta-agonists, is its very prolonged action due to the 70 to 80-hour half-life of its active metabolite. This characteristic is potentially an advantage in situations of advanced heart failure, for which repeated administrations of levosimendan might facilitate discharge from the hospital and prevent readmissions. A randomised controlled trial is currently under way to explore the efficacy and safety of intermittent levosimendan therapy, in addition to optimised standard therapy, in patients following hospitalisation for acute heart failure [10]. There are several other situations, in which levosimendan is proposed as a potential first-line choice instead of other classical inotropic agents: cardiogenic shock and weaning of veno-arterial ECMO, for example. Randomised controlled trials are currently being designed or in the process of being launched to test the hypothesis of its usefulness in patients with these conditions. With respect to the prophylactic use of the drug in patients with poor ventricular function undergoing cardiac surgery, the lack of effect observed in the LICORN and LEVO CTS trials raises several questions. First of all, the dose of 0.1 μg/kg/min might be considered insufficient, although a higher dose might have yielded a greater incidence of profound hypotension or postoperative atrial fibrillation. Second, the initiation of levosimendan infusion, at the time of anaesthesia induction, might be considered too close to the aortic clamping to allow for the full cardio protective effect of the drug. In addition, these trials have enrolled mixed cardiac surgical patients, including coronary artery bypass graft (CABG) alone and CABG combined with valve surgery. The combined surgery involves patient heterogeneity, which might, in turn, have blunted a possible beneficial effect. A recent preliminary subgroup analysis

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from the LEVO-CTS and LICORN trials suggested that the ''CABG alone'' population, as opposed to patients undergoing combined surgery, might indeed have a benefit in mortality with levosimendan versus placebo [11]. Of course, this is derived from subgroup analysis and, as such, just represents an exploratory finding. A first step would be to realise a meta-analysis on the individual data of the LEVO-CTS and LICORN patients to try to understand the factors responsible for this difference. If confirmed, this result would deserve another randomised controlled trial specifically targeting the patients with poor left ventricular ejection fraction (LVEF) undergoing CABG alone.

Meanwhile, physicians should refrain from using levosimendan as a first-line therapy in patients with heart failure, or as a prophylactic treatment in every surgical case with poor LVEF. However, they should remain ready to use it in the situations where beta-agonists are ineffective or associated with deleterious side effects, or whenever a benefit is expected for selected patients.

Disclosure of interest

Bernard Cholley: Orion laboratoiries provided the study drugs for the LICORN trial free of charge.

I have received honoraria from Orion Laboratories for giving lectures at industry-sponsored symposia and for being the president of an advisory board working for this company.

Thibaut Caruba declares that he has no competing interest.

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Bernard Cholley MD, PhD[a,b,*], Thibaut Caruba Pharm D[a]

[a]*Service d'anesthésie-réanimation, hôpital européen Georges-Pompidou, AP–HP, 20, rue Leblanc, 75015 Paris, France*

[b]*Université Paris Descartes, Sorbonne Paris Cité, Paris, France*

[*]Corresponding author at: Service d'anesthésie-réanimation, hôpital européen Georges-Pompidou, AP–HP, 20, rue Leblanc, 75015 Paris, France

E-mail address: bernard.cholley@aphp.fr (B. Cholley).