

Is there a place for levosimendan in the intensive care unit?

David C Simes

TO THE EDITOR: As refreshing as it is to see a clear final statement in a potentially complex review, it was courageous of Delaney and colleagues to conclude that levosimendan has no place in the intensive care unit based on five largely coronary care studies.¹ The fact that most of the cited studies purported to show a clear mortality benefit for the now “homeless” drug makes the authors’ dogmatic conclusion all the more awkward.

Presumably, Delaney et al were throwing out a line to biting fish when they claimed that “there is no place for levosimendan in the ICU”. Their paradoxical conclusion is based on three studies showing mortality benefits for levosimendan — one of them strikingly — and two more studies in which improvements in survival for subsets of mostly coronary care patients failed to reach statistical significance.

Noradrenaline, adrenaline, dobutamine, dopamine and oxygen all fall into weaker categories of scientific support in intensive care, and hopefully the authors will publish points of view along these lines!

The reductions in mortality found in the RUSSLAN² and LIDO³ studies were strangely denigrated (“early studies are often refuted by later studies”), the CASINO trial⁴ ridiculed because it showed such a great survival advantage for levosimendan that it had to be stopped, and the REVIVE trial⁵ using levosimendan *largely excluded ICU patients* yet was held up to support a point of view that it was no good for the patients it had excluded! What the . . .?

SURVIVE⁶ showed only a trend towards better survival for levosimendan-treated patients with primary cardiac failure. And was the best pillar for the dramatic conclusion.

Is it 1 April? Have I missed something? Or might there be a niche for an agent that, unlike our cheap and ubiquitous catecholamines, appears to improve myocardial performance without promoting ischaemia?

Should we avoid a drug that appears to have a catecholamine- and vasopressin-sparing effect, and improves cardiac output in subsets of patients with sepsis without generating myocardial ischaemia? Should the final conclusion stand, and a potentially effective agent in a subset of intensive care patients be withheld for 20 years until each

permutation of organ dysfunction has been unriddled to the satisfaction of the mighty *P* value?

And should noradrenaline, adrenaline, dobutamine and dopamine be withdrawn from use this minute to be subjected to the same scrutiny? Like all of our physiology-supporting agents, levosimendan can be used to achieve distinct clinical end-points. Patients are selected. Timing is vital. Ancillary supportive therapy is necessary. Together, the hope is to reduce mortality. But not by using a single tool in isolation, and we may never get a study showing a single agent improves mortality for a multiorgan illness.

To quote trials using a single agent as the primary panacea, pitched against placebo or an ischaemia-promoting toxin such as dobutamine in coronary care units, and then to pretend that those results are somehow relevant to the plethora of complex ICU patients is possibly misguided. One of my bosses used to say, “For every complex problem, there is a solution which is clear, simple and . . . wrong”. I think the conclusion of Delaney et al falls into that category.

Have they just reeled me in?

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