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Levosimendan

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Calcium sensitising has been proposed as the best way to improve deteriorating cardiac cell function in heart failure. However, it has proven difficult to develop agents which have a safe mode of action. To date, most agents evaluated in clinical trials also possess phosphodiesterase III and IV inhibitory activity, which may account for their adverse effects.

Levosimendan, a new drug in this class, improves central haemodynamic properties. Its action is dependent on the presence of calcium. In the presence of elevated filling pressures, levosimendan increases stroke volume, which is clear evidence of positive inotropy. Levosimendan increases cardiac output (10 to 40%) by this mechanism and, to some extent, by increasing heart rate (2 to 10%). Filling pressures are decreased significantly (20 to 40%) by levosimendan.

In clinical trials carried out to date, the effects of levosimendan have been shown to be rapid, with maximum effect reached in 10 to 30 minutes. Efficacy is sustained with 24- to 48-hour intravenous (IV) infusions and is dose dependent. After disappearance of the parent drug, improvements in haemodynamic properties appear to be prolonged by the presence of a long-acting levosimendan metabolite.

Safety is a constant concern with inotropic agents. The relatively extensive development programme for levosimendan, in which over 1000 patients have received the drug, has shown no association with a proarrhythmic effect. In individual cases, vasodilatation has caused a decrease in blood pressure and some patients experience headache, which is dose related. Lower mortality has been achieved in patients treated with levosimendan than in control or dobutamine-treated patients. Additional data are required on this important issue.

In conclusion, levosimendan induces extremely favourable haemodynamic effects in heart failure patients. So far no major safety concerns have been observed. On the contrary, prognosis in a small series of patients is improved after IV therapy of 6 to 24 hours. Levosimendan is a promising agent for the treatment of any kind of heart failure requiring IV treatment. An oral development programme is also underway. ▲