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Clinical trials with urodilatin in patients with acute decompensated heart failure

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Urodilatin belongs to the natriuretic peptide family and exerts its pharmacological effects via binding to the particulate guanylate cyclase A inducing intracellular increase of cyclic guanosine monophosphate (cGMP). Urodilatin is synthesized in the kidney and exhibits vasodilating, diuretic/natriuretic, and inhibitory effects on the renin-angiotensin-aldosterone-system. Ularitide is a synthetic version of urodilatin. Based on its pharmacological profile, Ularitide may present an ideal drug for the treatment of decompensated congestive heart failure (DHF). We investigated the pharmacodynamic effects of Ularitide in SIRIUS I (pilot project in 24 patients) and in SIRIUS II (proof-of-concept study) in 221 patients with DHF (inclusion criteria: CI ≤ 2.5 l/min per m^2, mean PCWP ≥ 18 mmHg). DHF patients were randomized equally to receive 7.5, 15, or 30 ng/kg/min Ularitide or placebo by continuous infusion over 24 hours. Ularitide significantly reduced right and left ventricular filling pressures in both studies. In SIRIUS II, PCWP significantly decreased at 6 hours: 7.5 ng: -6.5 ± 7.2; $p < 0.05$; 15 ng: -10.5 ± 6.3; $p < 0.01$; 30 ng: -10.1 ± 5.7; $p < 0.01$; placebo: -4.4 ± 6.1. Dyspnea score improved at 6 and 24 hours at all dose levels compared to placebo. The two higher Ularitide dose groups significantly decreased SVR. That produced an increase in cardiac index: placebo: 0.1 ± 0.3; 7.5 ng: 0.2 ± 0.4; $p < 0.05$; 15 ng: 0.3 ± 0.4; $p < 0.05$; 30 ng: 0.4 ± 0.5; $p < 0.01$. Haemodynamic improvement was accompanied by a significant reduction of elevated NT-proBNP in the 15 and 30 ng groups compared to placebo at 24 hours ($p < 0.05$). Systolic and diastolic blood pressure dose-dependently decreased in the two higher ularitide groups and diastolic BP decreased in all ularitide groups, while heart rate was unchanged. Main adverse events through day 3 were dose-dependent decreases in blood pressure/hypotension. Serum creatinine levels were unchanged during and over 2 days after end of ularitide infusion. Mortality rate through day 30 was higher in the placebo compared to ularitide 30 ng/kg/min group ($p < 0.05$). There were no differences in serious adverse events among the four treatment groups.

Conclusion

Ularitide infusions for 24 hours were well tolerated and resulted in dose-dependent favourable clinical and haemodynamic effects. Ularitide may have potential for the treatment of patients with DHF.