

POSTER PRESENTATION

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The novel dual GC-A and GC-B designer natriuretic peptide, cenderitide (CD-NP), enhances the renal actions of furosemide in a model of severe heart failure

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Background

Patients with congestive heart failure (HF) have symptomatic improvement with diuretic therapy, although with time diuretic resistance and renal dysfunction can occur. Cenderitide (also known as CD-NP), now in clinical trials in patients with HF, is a Mayo designed chimeric natriuretic peptide which, unlike the native natriuretic peptides (NPs) ANP, BNP and CNP, binds both to guanylyl cyclase (GC)-B and GC-A with greater affinity for GC-B. Cenderitide thus was designed to mediate more venodilation than arterial dilation via GC-B and so result in less hypotension than BNP or ANP, but unlike CNP also possess natriuretic and diuretic properties via GC-A activation. We tested the hypothesis that combining cenderitide with furosemide will produce increased diuresis and natriuresis compared to furosemide alone without causing excessive hypotension or renal dysfunction in experimental HF.

Methods

HF was induced in two groups of dogs ($n=3$ each) by tachypacing. On day 11 of pacing an acute study was performed under general anesthesia. The left ureter was cannulated and the renal artery was equipped with a flow probe. A continuous inulin infusion was started to measure glomerular filtration rate (GFR) and after equilibration a 30-minute baseline clearance (C1) was done. After that, one group (F+cenderitide) received a 105-minute cenderitide infusion (100 ng/kg/min), while furosemide (1 mg/kg) was administered over 60 minutes. After a 15-minute lead-in, three 30-minute clearances were done (C2, C3,

C4). For the other group (F) furosemide was administered together with vehicle instead of cenderitide. Changes from baseline were compared between groups by unpaired t-test. Values are mean \pm SEM. * $p<0.05$ between groups.

Results

F+cenderitide compared to F resulted in greater increases in sodium excretion* (+993 \pm 123 vs +426 \pm 98 μ Eq/min) and urine flow* (+8.5 \pm 0.8* vs +4.1 \pm 0.5 mL/min) in C2 and cumulatively from C2 through C4. GFR, renal blood flow and renal vascular resistance were similar between groups. Addition of cenderitide to F reduced right atrial pressure* but did not result in systemic hypotension.

Conclusion

Adding cenderitide to furosemide significantly increases natriuresis and diuresis as compared to furosemide alone. Also, compared to F alone F+cenderitide results in a greater reduction in cardiac preload without inducing systemic hypotension. These findings suggest that the combination of F+ cenderitide represents an innovative co-therapy to enhance renal response to diuretics and to augment preload reduction; therefore, warranting further studies in human HF.

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