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Pharmacokinetic and pharmacodynamic study of a novel chimeric natriuretic peptide, CD-NP, in the normal dog

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Background

CD-NP is a novel Mayo-designed cGMP-activating chimeric natriuretic peptide (NP) that consists of the 22-amino-acid (AA) residues of C-type natriuretic peptide (CNP) and the 15-AA C-terminus of *Dendroaspis* NP [1]. The rationale for its design was to transform CNP, a cardioprotective peptide with limited renal actions, into a chimeric peptide with both cardiovascular and renal effects. Previous studies from our laboratory have demonstrated that CD-NP was natriuretic, diuretic, cardiac-unloading, and renin-suppressing [1]. In this investigation, we studied the pharmacokinetics (PK) of CD-NP for the first time and further evaluated its pharmacodynamic profile *in vivo*.

Materials and methods

CD-NP 50 ng/kg/min was administered as a continuous i.v. infusion for 75 minutes to ten normal anesthetized dogs. Four 30-min clearances were performed: pre-infusion, 30-min of infusion (I), 60-min I, and post-I. Glomerular filtration rate (GFR) was measured by inulin clearance. Comparisons of cardiorenal and neurohormonal parameters were made within group *versus* pre-I (mean ± S.E.M., $P < 0.05$*, <0.01†). For PK study (n = 4), blood was collected at baseline, at 25th, 30th, 45th, 60th, and 75th min during infusion (I); and at 1st, 2nd, 4th, 6th, 10th, 20th, 30th, 45th, 60th min post-I. An established CNP radioimmunoassay was employed to detect plasma CNP immunoreactivity, as an estimate for CD-NP levels. Non-compartmental PK analysis was performed (WinNonlin version 5.2, Pharsight Corporation, CA).

Results

The elimination half-life of CD-NP was 18.4 ± 1.4 min, volume of distribution (V_D) based on the terminal phase was 3.1 ± 1 L/kg, steady-state V_D was 1.6 ± 0.5 L/kg and total body clearance was 111 ± 32 ml/min/kg. The maximum observed concentration was 1183 ± 388 pg/ml and time to maximum observed concentration was 48.8 ± 11.3 min. CD-NP increased urine flow (0.23 ± .06 to 1.81 ± .26† ml/min), urinary Na^+ excretion (18.6 ± 3.7 to 237 ± 26† meq/min), and GFR (37 ± 2 to 53 ± 4† ml/min). These renal actions were associated with an increase in net renal cGMP generation (705 ± 143 to 4194 ± 770† pmol/min). Proximal and distal fractional reabsorption of Na^+ decreased (75 ± 2 to 57 ± 3†%; 98 ± .2 to 92 ± 1†%, respectively). Urinary K^+ excretion increased (26.4 ± 3.7 to 64.1 ± 4.3† meq/min). Decreases in pulmonary arterial pressure (11.7 ± .6 to 10.3 ± .4* mmHg), pulmonary capillary wedge pressure (5.7 ± .7 to 3.2 ± .7† mmHg), and right atrial pressure (1.9 ± .4 to 0.9 ± .5† mmHg) were observed with no significant change in systemic blood pressure. At the end of CD-NP infusion, there was no significant change in heart rate (120 ± 8 *vs* 110 ± 8 bpm pre-I) or the QT_c interval (310 ± 9 *vs* 309 ± 9 msec pre-I). An increase in hematocrit (36 ± .9 to 38 ± .6†%) was noted.

Conclusion

CD-NP exhibits a favorable pharmacologic profile in normal dogs without induction of systemic hypotension. Its therapeutic potential as a novel drug for the treatment of

heart failure and other cardiorenal disease states warrants further investigation.

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References

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