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Coadministration of B-type natriuretic peptide and the vasopressin-2 receptor antagonist tolvaptan: a novel physiologic strategy to enhance water and sodium excretion without adversely affecting renal or neurohumoral function in experimental congestive heart failure

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Background

Efficacy of diuretic therapy in congestive heart failure (CHF) can be affected by renal hemodynamics, neurohumoral activation, and diuretic-induced changes in renal function. Physiological strategies that enhance water and sodium (Na) excretion while maintaining renal function are a high priority. Arginine vasopressin increases water reabsorption after binding to the V2 receptor in the collecting duct (CD). In contrast, B-type natriuretic peptide (B) decreases Na reabsorption via the particulate guanylyl cyclase linked natriuretic peptide A receptor (NPR-A) also in the CD. We hypothesized that coadministration of the V2-receptor antagonist tolvaptan (T) and B would mediate a diuresis and natriuresis without adversely affecting renal hemodynamics in experimental CHF.

Methods and results

Severe CHF was induced in 3 groups of dogs by tachypacing. On day 11 cardiorenal function was assessed. After baseline measurements, one group received T alone (0.1 mg/kg IV bolus; n = 6), one received infusion of B (50 ng/kg/min; n = 6) and one received both drugs (n = 5). Changes from baseline were compared with 1-ANOVA. *p < 0.05. Mean arterial pressure increased with T, decreased with B, and was unchanged with T+B (+5 ± 1 vs -14 ± 1 vs -1 ± 1 mmHg, *between groups) with renal perfusion pressure paralleling changes in mean arterial pressure. Pulmonary capillary wedge pressure was unchanged with T and decreased with T+B, but more so with B alone (*B vs T, T+B). Renal blood flow and glomerular filtration rate (GFR) were preserved in all groups. Increase in urine flow was greatest with combined V2 antagonism with T and NPR A activation with B (T, B, and T+B: +0.4 ± 0.1 vs +0.9 ± 0.4 vs +2.4 ± 0.5 mL/min, *T+B vs T, B). Electrolyte-free water excretion was higher with T+B compared to T and B*. T was not natriuretic, whereas B and T+B were (+0 ± 0 vs +76 ± 40 vs +28 ± 10 Eq/min, *T vs B, T+B). Distal fractional Na reabsorption increased with T, but not with B and T+B*. Decreases in proximal fractional Na reabsorption occurred only with B* and T+B*. Plasma renin activity was unchanged with T, but suppressed with B and T+B (*T vs B) while aldosterone which was increased with T and B, was suppressed by T+B (*T vs T+B).

Conclusion

Coadministration of tolvaptan and BNP enhanced urine flow and electrolyte-free water excretion greater than either alone demonstrating a novel mechanism for

aquaresis in CHF by co-targeting of the V2 and NPR-A receptor in the CD and linked in part to inhibition of proximal tubular sodium and water reabsorption during co-administration. Unlike tolvaptan alone, co-administration with BNP also induced a natriuresis. Whereas tolvaptan increased and BNP decreased mean arterial and renal perfusion pressure, tolvaptan and BNP coadministration had a neutral effect. Thus, tolvaptan and BNP coadministration may be an important and novel physiologic strategy to counter sodium and water retention in CHF.