Effect of Intense Angiotensin II Suppression on the Diuretic Response to Furosemide During Chronic ACE Inhibition

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Background  Contrary to expectation, most studies have demonstrated that initiation of an angiotensin-converting enzyme (ACE) inhibitor in conventional doses in patients with heart failure reduces the diuretic efficacy of furosemide. Recently, it has been suggested that single low doses (1 mg) but not high doses (25 mg) of captopril enhance furosemide-induced diuresis. It is not known whether the interaction between diuretics and ACE inhibitors are altered during long-term dosing.

Methods and Results  Eight patients with heart failure treated with diuretics and ACE inhibitors for at least 3 months were studied. All patients were established on captopril 12.5 mg three times daily for 2 weeks before the study. Sodium intake was fixed before the study, and usual medication was withheld on study days. Intravenous furosemide was given on each of 2 study days to maintain a moderate, constant diuresis. Renal plasma flow and glomerular filtration rate (GFR) were determined using clearance techniques, and urine was collected hourly over 4 hours. Captopril 12.5 mg or placebo was given in a randomized, single-blind fashion at the end of the first hour. Compared with placebo, captopril reduced plasma concentrations of angiotensin II (23±18 versus 4±3 pg/mL, 1 hour after dosing, P<.02) and systolic (131±31 versus 122±29 mm Hg, P<.01) and diastolic (74±15 versus 67±13 mm Hg, P<.05) blood pressures. GFR fell (55±24 versus 51±22 mL/min, P<.02) and effective renal plasma flow rose during the first (198±76 versus 231±49 mL/min) and second hours after dosing (185±69 versus 247±74 mL/min, P<.02). Similarly, urine volumes, in response to furosemide, increased after captopril (238±90 versus 283±111 mL, P<.05, and 245±78 versus 311±92 mL, P<.01, 1 and 2 hours after dosing).

Conclusions  Intense although transient ACE inhibition with captopril enhances the diuretic effects of furosemide during long-term ACE inhibition. (Circulation. 1994;90:220-224.)

Key Words  furosemide  angiotensin  heart failure

The treatment of congestive cardiac failure with diuretics is associated with activation of the renin-angiotensin system. Angiotensin II, both circulating and produced locally in the kidney, has a number of direct and indirect actions on renal function. Suppression of angiotensin II in the circulation and/or renal tissues should increase sodium loss either by withdrawing a direct sodium-retaining effect of angiotensin II on the renal tubule or by reducing plasma concentrations of aldosterone. However, most patients with heart failure still do not fail to reduce their diuretic requirement but tend to retain fluid and sodium in the days after initiation of an angiotensin-converting enzyme (ACE) inhibitor despite a clear reduction in circulating levels of both angiotensin II and aldosterone. Although the direct renal effects of suppression of angiotensin II and aldosterone predict that a natriuresis should occur, ACE inhibitors also reduce arterial pressure, plasma natriuretic peptides, and glomerular filtration rate (GFR), actions that favor salt and water retention.

Measurement of weight and total body sodium suggest that ACE inhibitors have a neutral effect on water and sodium balance over 6 to 8 weeks, indicating reversal of the initial trend.

A recent study indicated that in the acute setting, larger doses of captopril, associated with a fall in GFR, impaired the natriuretic response to furosemide, whereas natriuresis was augmented by a dose of 1 mg. However, the interaction of diuretic agents and ACE inhibitors during long-term combined therapy has not been addressed. The balance between effects on arterial pressure and GFR, attenuating the diuretic effects of furosemide, and reductions in aldosterone and angiotensin II, favoring a greater diuresis, will determine the final outcome.

The present study was undertaken to compare the renal effects of furosemide during short-lived periods of intense angiotensin II suppression with a period when circulating angiotensin II had returned to baseline in patients with chronic heart failure established on ACE inhibitor therapy.

Methods

Patients

Eight patients (seven men and one woman) aged 49 to 72 years (mean, 65) with chronic heart failure due to left ventricular systolic dysfunction were studied. All had an ejection fraction of <30% on radionuclide ventriculography or a frac-

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tional shortening of <20% on echocardiography. Four patients were classified as New York Heart Association class II and four as class III. The mean dose of furosemide was 90 mg/d (range, 80 to 160 mg/d). All had been taking ACE inhibitors for at least 3 months and had changed to captopril 12.5 mg TID 2 weeks before inclusion in the study.

**Study Protocol**

Patients adhered to a diet containing 40 mmol/L of potassium and 100 mmol/L of sodium per day for 3 days before each study. Each patient was studied twice, not less than 48 hours apart. Usual medications and caffeine-containing beverages were omitted on the study days.

Bolus doses of inulin (50 mg/kg) and para-aminohippurate (PAH, 800 mg) were administered by infusion of the above at 32.5 mg/min and 30 mg/min, respectively, for the duration of the study.

An intravenous bolus of furosemide 5 mg was given, and patients rested supine for 30 minutes before passing urine. Subsequent hourly boluses of furosemide (3 to 5 mg/h, depending on usual daily dose of furosemide) were given in identical fashion to maintain a steady moderate diuresis. Heart rate and arterial pressure were measured half hourly. Urinary and insensible losses were replaced hourly with water. Hourly blood samples were taken for estimation of plasma hormones, electrolytes, PAH, and inulin. Urine was collected hourly for estimation of PAH, inulin, electrolytes, guanosine-3',5'-monophosphate (cGMP), and furosemide. At the end of the first hour, 12.5 mg of captopril or placebo was given orally in a randomized, single-blind fashion.

Heart rate was counted from the apex, and supine arterial pressure was measured using a mercury sphygmomanometer.

**Plasma concentrations of active renin, angiotensin II, and aldosterone and urinary concentrations of cGMP** were measured by radioimmunoassay, as previously described. Plasma and urinary electrolytes and creatinine were measured using standard automated procedures (Bayer Diag SMAC-2, Technicon and Beckman E2A ISE analyzers, respectively).

Plasma and urinary PAH were measured using the colorimetric method of Waugh and Beall. Plasma and urinary inulin were measured using the colorimetric method of White and Samson. Renal clearance of inulin was used as a measure of GFR and renal clearance of PAH as a measure of effective renal plasma flow.

**Urineary concentrations of furosemide** were determined using a spectrofluorometric high-performance liquid chromatography method. Internal standard (bumetanide, 250 ng) was added to 0.25 mL of urine, which was subsequently made up to 1 mL with distilled water. The samples were mixed and centrifuged at 6000 rpm to remove any particulate matter. The supernatant was injected (30 μL) via an autosampler (WISP 710B, Waters Millipore) onto a 25-cm mixed alkyl-cyano-bonded reverse-phase column (Sherisorb 5 μm ODS/CN, PhaseSep). The peaks were eluted with an isocratic buffer (0.1 mol/L H3PO4 to CH3CN; 50:50, pH 3.5, with NaOH) pumped at 1 mL/min. Furosemide (5.5 minutes) and bumetanide (8.5 minutes) peaks were detected with a Kratos FS970 fluorometer (Applied Biosystems; excitation wavelength, 220 nm, emission cutoff at 379 nm) and quantified with an integrator (model SP4270, Spectra Physics) using peak height ratios. The urinary furosemide curve was linear from 150 to 5000 ng/mL with intra-assay and interassay coefficients of variation of 1% and 7%, respectively. With the exception of patients on nifedipine, whose urine samples exhibited multiple peaks, none of the other drugs tested concomitantly interfered with determination of furosemide.

**Statistical Tests**

Differences between treatment schedules were tested for significance using ANOVA. For normally distributed data, the Student's two-tailed t test was used to compare individual time points. For nonparametrically distributed data, a Wilcoxon matched-pairs, signed-ranks test was applied. Bonferroni's correction was made for multiple comparisons.

**Results**

Urine volume (Fig 1), sodium excretion (Fig 2), and chloride excretion (Fig 3) increased in the 2 hours after captopril. The ratio of urinary sodium to creatinine (62.5±9.5 to 80.0±13.5 and 61.0±9.3 to 74.5±12.2 mmol/mmol, P<.05, and 1 and 2 hours after placebo and captopril, respectively) was greater after captopril compared with placebo, and the ratio of sodium to potassium increased (4.6±1.2 to 5.1±1.3 mmol/mmol, P<.05, at 2 hours after dosing). The ratio of sodium to phosphate (24.1±3.9 to 34.5±7.6 and 20.5±2.8 to 26.5±3.8 mmol/mmol, P=NS) did not change.

Systolic and diastolic blood pressures declined 1 hour after captopril (P<.01 and P<.05, respectively). Heart rate was unchanged (Fig 4).

GFR fell 1 and 2 hours after captopril compared with placebo. Effective renal plasma flow rose and filtration fraction fell after captopril; the most pronounced effects were observed in the 2 hours after dosing (Fig 5).

Plasma concentrations of angiotensin II were suppressed maximally (<5 pg/mL; normal range, 2 to 12) 1 hour after captopril and gradually increased thereafter, although baseline values were not reached during the time course of the study. Plasma concentrations of aldosterone fell throughout the study in both groups but
were consistently lower in the captopril-treated group. Plasma active renin concentration rose 1 hour after captopril and remained elevated throughout the study (Fig 6). Urinary concentrations of cGMP nor furosemide were altered by captopril.

**Discussion**

We have shown that in patients with heart failure treated chronically with ACE inhibitors, salt and water excretion in response to furosemide is enhanced by suppression of angiotensin II. This contrasts with the findings during initiation of ACE inhibitor therapy in patients with heart failure, in whom the diuretic effect of furosemide is usually reduced by ACE inhibition.3-7

The present study gives some insight into the site of the renal effects of captopril on sodium handling. The increased natriuresis induced by captopril in the present study was due to reduced tubular reabsorption of sodium, since GFR fell and the ratio of sodium to creatinine increased. Most phosphate reabsorption occurs in the proximal tubule. Excretion of sodium relative to phosphate did not change after captopril, suggesting that a fall in sodium reabsorption at this site contributed to the natriuresis; however, uncoupling of proximal tubular handling of sodium and phosphate after a loop diuretic has been described.14 We demonstrated an increase in the ratio of sodium to potassium excretion suggesting that distal sodium reabsorption decreased, associated with the fall in plasma concentrations of aldosterone, contributing to the natriuresis.

Increased delivery of furosemide to its receptor site in the ascending limb of the loop of Henle after renal vasodilatation might account for the potentiation of the diuresis by captopril. Furthermore, captopril has been reported to impair the renal tubular secretion of furosemide.15 However, we observed no increase in the urinary excretion of furosemide after administering captopril.

ACE inhibitors have effects on both parasympathetic and sympathetic tone and alter baroreceptor function.16,17 Arterial pressure is a powerful determinant of renal salt and water handling, and each individual appears to operate around a "set point" relating these
variables. It is possible that chronic but not acute ACE inhibition alters the relation between pressure and natriuresis, accounting for the reversal of the initial tendency for fluid retention.

Angiotensin II exerts powerful vasoconstrictor effects on the renal vasculature; the efferent arteriole is particularly sensitive to its effects. Reduction of blood flow by angiotensin II in the vasa recta that descend into the renal medulla may increase salt and water reabsorption, and captopril could reverse this,1,2 diverting global flow to the more superficial cortical nephrons.

Captopril enhances intrarenal production of prostaglandins, either directly or through increases in bradykinin,18 which may be important in preventing more profound falls in glomerular filtration than those actually observed after ACE inhibition. This protective effect on glomerular filtration is presumably due to changes in afferent arteriolar tone or glomerular function itself.19 Renal prostaglandins also may increase salt and water excretion by enhancing renal tubular sodium transport20 or by opposing the actions of antidiuretic hormone in the collecting duct.21 Furosemide also stimulates renal synthesis of prostaglandin E2 either directly or by enhancing production of bradykinin.22-24 Administration of agents such as indomethacin impairs GFR and promotes sodium retention in patients with heart failure,25 supposedly by inhibiting renal cyclo-oxygenase and prostaglandin production, an effect that is more pronounced in patients with heart failure treated with diuretics and ACE inhibitors.26 Therefore, increased renal prostaglandin production, possibly in synergy with furosemide, could be responsible for the effects of captopril on salt and water excretion.

A decline in filtration fraction is one of the most consistent hemodynamic responses to an ACE inhibitor.1 Effective renal plasma flow was increased after administration of captopril; GFR and hence filtration fraction was reduced. The time course of the effects of captopril on plasma concentrations of angiotensin II and on filtration fraction were remarkably similar. This suggests either that efferent arteriolar tone, a major determinant of filtration fraction, is regulated mainly by the circulating renin-angiotensin system or that changes in tissue and circulating renin-angiotensin systems in response to captopril are closely related.

Implications for the Optimal Therapeutic Dose of ACE Inhibitors

The dose of captopril used in our study was chosen to achieve powerful suppression of angiotensin II concentrations for some hours but allowing the concentrations to recover toward the end of the study period. A larger dose of captopril would be unlikely to produce more intense suppression of circulating angiotensin II, although the duration of suppression of angiotensin II would have been longer. Although recent studies support the use of larger doses of ACE inhibitors in patients with heart failure,27 in clinical practice, many patients are maintained on doses of this magnitude.

These data suggest that intense ACE inhibition either by frequent administration or by larger doses of ACE inhibitor may enhance furosemide-induced diuresis as well as prevent diuretic-induced increases in angiotensin II. This may explain preliminary evidence that suggests that high-dose ACE inhibition is more effective than low-dose ACE inhibition in heart failure in terms of symptoms and possibly prognosis.17,27,28 An enhanced diuresis observed with high-dose ACE inhibition, by causing a degree of prerenal uremia, also may contribute to the greater increase in plasma urea observed with long-acting ACE inhibitors.26

Study Limitations

We did not measure atrial natriuretic peptide (ANP) or bradykinin. Rouleau et al29 suggested that the relation between plasma concentrations of ANP and atrial pressure are altered by ACE inhibition such that for a given pressure, a higher plasma concentration of ANP exists. However, this resetting of the relation between ANP and atrial pressure appears to be related to long-term rather than short-term ACE inhibitor effects, and it is not clear that increases in ANP concentrations will enhance furosemide-induced diuresis in patients with heart failure.30 Intense ACE inhibition may potentiate the effects of bradykinin on renal medullary blood flow and thus promote diuresis. In addition, ACE inhibitor therapy has been shown to result in delayed reduction in circulating arginine vasopressin concentrations, which would favor diuresis and natriuresis,5,6 but we did not measure it in this study. This study is not directly applicable to clinical practice because furosemide was given intravenously and captopril was used in a dose that would be considered subtherapeutic by many. However, for the purpose of looking at the
mechanisms of ACE-inhibitor effect, the use of intravenous furosemide to overcome variable oral absorption appears preferable. Lower than recommended doses of captopril were used so that patients could be studied at times when ACE inhibition was no longer effective in suppressing angiotensin II; however, it should be noted that less than a third of all prescriptions for captopril are for 12.5 mg TID or less.

Conclusions

Short-term inhibition of ACE in patients with heart failure has been shown to reduce the diuretic efficacy of furosemide. In contrast, we have shown that in patients treated chronically with ACE inhibitors, the natriuretic and diuretic responses to furosemide are enhanced by intense suppression of angiotensin II. The precise renal mechanism for this effect remains to be disclosed, but altered baroreceptor function with a change in the “set point” for sodium is possible. The implications of these findings as to the optimal dosing regime for ACE inhibitors should be resolved by ongoing studies.

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