MONDAY, APRIL 26, 1982
PM
CLINICAL TRIAL OF VASODILATORS IN HEART FAILURE
4:00-5:15

CAPTOPRIL PHARMACOKINETICS IN CHRONIC HEART FAILURE: CORRELATION WITH ACUTE HEMODYNAMIC AND HORMONAL RESPONSE. Robert J. Cody, MD; Andrew Covit, MD; Gary Schaer, MD; Gary Williams, MD. Cornell University Medical Center New York, N.Y.

There is no pharmacokinetic data regarding acute response to captopril (CAP) in congestive heart failure (CHF), and absence of response might represent inadequate dosage or minimal renin-angiotensin system (RAS) activity. We therefore correlated the response of the RAS and hemodynamic change with CAP blood levels in six patients after a 25 mg. oral dose. Blood levels (ng/ml) were: 26 (.33 hr.), 58 (.67 hr.), 81 (1.0 hr.), 65 (1.5 hr.), 51 (2.0 hr.), 24 (3.0 hr.), 10 (4.0 hr.), and 0.7 (8.0 hr.). For the group, maximum concentration was 99±19 at 1.2±.2 hr. Decrease of AP (78±3 to 66±6 mm Hg.), PWP (20±3 to 12±3 mm Hg.), SVR (1492±184 to 1223±195 d/s/cm^{-5}), and increase of CI (2.09±.15 to 2.39±.14 L/min/M^2), and SI (28±3 to 34±4 ml) occurred at 1.0 hr. These return to baseline by 4.0 hr. Compared with control values, plasma renin (ng/ml/hr) was increased (8±3 to 44±10), and plasma aldosterone (ng %) decreased (10±2 to 6±1) at 1.0 hr.; both p<.05. However, extent of hemodynamic improvement was correlated with baseline plasma renin: AP (r=.-780), PWP (r=-.606), SVR (r=-.856), SI (r=.727). In summary, oral CAP is readily absorbed in CHF, with peak levels at 1.2 hr. Levels correlated with hemodynamic effects and RAS blockade. However, baseline RAS activity was a better predictor of the extent of response; patients with minimal activity showed minimal hemodynamic improvement despite adequate blood levels.

CONTROLLED TRIAL OF CAPTOPRIL FOR HEART FAILURE: EFFECTS ON HEMODYNAMICS, SCINTIGRAPHY AND EXERCISE TOLERANCE. Barry Kramer, MD, Barry Massie, MD, FACC, Nina Topic, RN. VA Hospital and University of California San Francisco, CA.

To rigorously assess the efficacy of captopril (CAP) in chronic heart failure (CHF), we measured the acute effect of open label (OL) CAP on hemodynamic (HEMO) and scintigraphic (SCINT) indices in 12 patients (PTS) with Class 3 CHF maintained on digoxin and diuretics. Then, in a double-blinded 3 month (3M) trial, 7 PTS were randomized to CAP, 12.5-100 mg tid (Group 1) and 5 to placebo (PL, Group 2). Serial SCINT, upright bicycle exercise (Ex) tests and repeat HEMO (in 9/10 survivors) were performed.

	LVFP	SVI	EF	EDV	VO_2(ml/kg)	ExDur(min)
GP1-pre	25±10	28±9	20±7	417±62	11.8±2.6	8.6±2.1
CAP-OL	16±8#	36±7*	23±6#	371±74*	12.3±2.3	9.1±1.9
CAP-3M	16±7#	34±7#	24±8#	377±79*	15.6±2.7*	11.8±1.3#
GP2-pre	30±5	19±6	18±5	369±86	11.1±2.5	6.8±1.0
CAP-OL	18±6	30±9*	21±4*	338±71*	11.1±1.7	5.7±1.8
PL-3M	29±5	18±5	17±6	363±84	10.3±3.6	5.9±4.8

Significant change from control: *=p<.05; #=p<.01

Acutely, OL CAP reduced left ventricular filling pressure (LVFP) and increased stroke volume index (SVI) in both groups. LV ejection fraction (EF) rose slightly, while LV end diastolic volume (EDV) declined. Maximum VO_2 did not change concurrently with this acute hemodynamic improvement. After 3M LVFP remained lower and SVI higher in PTS on CAP, but not in PL PTS. The acute improvement in EF and EDV also was sustained only in PTS on CAP. PTS on CAP exhibited an increase in Ex duration and a corresponding rise in maximum VO_2 at 3M, while exercise tolerance did not change on PL. Three PTS markedly worsened on PL, one of whom died suddenly and a second who died shortly after being withdrawn from the study. These findings demonstrate the acute efficacy and long term benefits of CAP therapy for CHF.

THE EFFECT OF CAPTOPRIL ON SYSTEMIC AND RENAL HEMODYNAMICS IN PATIENTS WITH CONGESTIVE HEART FAILURE. Eric R. Powers, MD; Jane E. Stone, MD; Kenneth S. Bannerman, MD; Dennis S. Reison, MD; Melvin B. Weiss, MD, FACC; Robert R. Sciacca, EngScD; Paul J. Cannon, MD, FACC, Columbia University, New York, N.Y.

Recent studies have demonstrated that Captopril (C), an oral angiotensin converting enzyme inhibitor, can improve renal perfusion and function in patients with congestive heart failure (CHF). We studied the effects of C on systemic and renal hemodynamics, and sodium excretion in nine patients with CHF. Systemic hemodynamics were measured before and one hour after a 25mg oral dose of Captopril. Creatinine clearance, renal blood flow (I^{131}-hippuran clearance) and sodium excretion were measured the day before and the day after initiation of therapy. The results are given below (mean ± SD).

	Pre	Post
heart rate (beats/min)	75±13	73±16
cardiac output (L/min)	3.6±1.0	4.2±1.3*
pulmonary artery pressure (mmHg)	31±8	23±10*
pulmonary wedge pressure (mmHg)	18±6	12±9*
arterial pressure (mmHg)	77±10	59±13*
systemic vascular resistance (dyne-sec-cm^{-5})	1706±616	1225±542
creatinine clearance (ml/min)	58±24	62±34
renal blood flow (ml/min)	387±251	345±147
filtration fraction	.19±.08	.19±.09
sodium excretion (meq/day)	39±39	26±17

*significant change with Captopril (p<.05)

Thus, despite a significant improvement in systemic hemodynamics, C did not result in a change in filtration fraction, an improved sodium excretion or a redistribution of the cardiac output toward the kidney. These data demonstrate that Captopril may not improve renal hemodynamics and function in all patients with CHF.

CHRONIC ADJUNCTIVE TRIMAZOSIN VASODILATOR THERAPY IN HEART FAILURE: A SIX MONTH DOUBLE-BLIND PLACEBO CONTROLLED RANDOMIZED TRIAL
Philip C. Kirlin, MD; Sunil Das, MD; Theresa Johnson, RN; Mary Kay Foley, RN; Ka Lo, MD; Bertram Pitt, MD, FACC, University of Michigan, Ann Arbor, Michigan

Trimazosin(T) is an alpha-blocking vasodilating agent with demonstrated benefit for up to 2 months(mo) in heart failure(HF). In order to assess longer term effects of T, 16 patients(pts) with chronic functional class II-III HF despite digitalis and diuretic were randomized to 6 mo double-blind adjunctive T(n=8) or placebo(P)(n=8) with simultaneous noninvasive radionuclide and invasive hemodynamic assessment. CI(L/min/m^2), PA wedge pressure(PAW)(mmHg), LV ejection fraction(LVEF)(%), LV end-diastolic and end-systolic volume index(EDVI,ESVI)(ml/m^2) and systemic vascular and pulmonary arteriolar resistance index(SVRI,PARI) (dsc^{-5}/m^2) were determined at supine rest(R) and maximal bicycle ergometer exercise(E): (x̄±SD; *=p≤.05, paired t)

	T		CI	PAW	LVEF	EDVI	ESVI	SVRI	PARI
Base-line		R	2.5±.4	18±9	19±4	156±33	128±30	2939±394	402±89
		E	4.3±1	34±9	21±13	206±109	173±105	2097±360	390±188
6 mo		R	2.4±.6	18±13	24±9	140±45	108±43	3203±645	397±179
		E	4.5±1	29±9*	26±10*	144±46*	110±46*	2022±361	417±258
	P								
Base-line		R	2.4±.4	17±9	30±14	122±46	90±44	3235±831	371±283
		E	4.7±2	37±8	26±10	150±62	114±80	2238±966	281±242
6 mo		R	2.6±.8	18±9	28±15	174±53	131±60	3404±1999	436±462
		E	5.2±1	25±11*	28±13	164±51	123±61	1807±330	285±202

T pts received significantly greater diuretic dose increases compared to P (+97% vs -8%, p<.03) to maintain stable body weight.
Thus, adjunctive T improved E but not R hemodynamics at 6 mo compared to digitalis and diuretic alone.