Wednesday, March 6, 1991
Poster Displayed: 9:00AM–12:00NOON
Author Present: 9:00AM–10:00AM
Hall F, West Concourse
Clinical Pharmacology—Heart Failure/Mechanisms

MECHANISM OF ACTION OF CARVEDILOL IN HUMAN VENTRICULAR MYOCARDIUM. Wayne Minobe, Patti Larrabee, Michael R. Bristow. University of Utah, Salt Lake City, UT

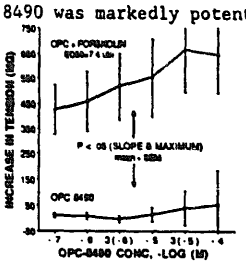
Carvedilol (C) is a new ß-blocker/vasodilator that is undergoing clinical trial for heart failure treatment. Data from animal screens suggest that C is a non-selective ß-blocking agent with vasodilator properties due to α-blockade. Because of species differences in animals vs human adrenergic receptor pharmacology, we have characterized the ß- and α-blocking activity of C in preparations derived from nonfailing (NF) and failing (F) human ventricles and compared the results to the selective $ß_1$ blocking agent metoprolol (M) and the nonselective ß blocker/vasodilator bucindolol (B). Results of radioligand-cold ligand competition curves (CC) performed in crude myocardial membranes with and without $3x10^{-5}$M Gpp(NH)p (G) were: (values ± SEM)

ß rec	CC:	Curve	IC_{50},nM	IC_{50},nM	K_H,nM	K_L,nM	$\alpha_1 K_I$,nM
Group	Drug	Slope	(no G)	(+G)	(+G)	(+G)	(no G)
F	C	.72	12.2	135*	4.8	208	10.9
(69/31	n=10	±.04	±8.9	±79	±2.3	±102	±5.2
$ß_1/ß_2$)	M	.58	1311	1107	11.9	3711	-
	n=5	±.10	±920	±767	±3.1	±203	
	B	.81	11.0	44.8*	5.4	-	249
	n=4	±.11	±3.3	±18.6	±2.2		±125
NF	C	.90	14.2	24.1	7.5	-	-
(84/16)	n=4	±.02	±5.0	±12.2	±.5	-	-

Conclusions: 1) For C the $ß_1$ receptor affinity (K_H) is 2.5 times > and the $ß_1/ß_2$ selectivity ratio is 6 times < M. 2) As does B, C exhibits an "agonist" binding site modulated by guanine nucleotides that does not confer ISA. 3) The α_1 blocking activity of C is 23 fold > that of B, and approaches the $ß_1$ blocking activity of C. The selective $ß_1$ and α_1 blocking properties of C presumably explain why this agent is extremely well tolerated in subjects with advanced heart failure.

EVIDENCE FOR PHOSPHODIESTERASE INHIBITORY ACTIVITY OF OPC 8490 IN THE FAILING HUMAN HEART. Amelia Focaccio, Wayne Minobe, Matthew A. Movsesian, Judith Krall, George Peeters, Yutaka Eki, Michael R. Bristow. University of Utah, Salt Lake City, UT

OPC 8490 is a water soluble quinolinone derivative whose properties in animal systems include positive inotropic effects and prolongation of action potential. Various mechanisms of action for the positive inotropic response of the quinolinones have been suggested, including K^+ and/or Na^+ channel activity and cAMP phosphodiesterase (cAMP PDE) inhibition. In the present study OPC 8490 effects on 1) cAMP PDE III; 2) inotropic response in right ventricular trabeculae (RVT) in the presence (n=17) and absence of forskolin (n=18); and 3) RVT action potential were assessed in preparations taken from failing human hearts (FHH). The drug inhibited cAMP PDE in a concentration-dependent manner with an IC_{50} of 12.0 µM; the IC_{50} for the cAMP PDE inhibitor enoximone was 3.6 µM. OPC 8490 at 10^{-8} to 10^{-4}M produced a marginal increase in isometric systolic tension in RVT. After administration of a minimally effective dose of forskolin to elevate intracellular cAMP levels the inotropic response to OPC 8490 was markedly potentiated as shown in the figure, indicating PDE inhibition. In RVT OPC 8490 induced an action potential prolongation by 71±3%, with an EC_{50} of 9.3 µM. Conclusions: The positive inotropic effect of OPC 8490 in FHH is due at least in part to cAMP PDE inhibition; the contribution of action potential prolongation to the inotropic effects remains to be determined.



XAMOTEROL HAS AGONIST ACTIVITY IN END-STAGE FAILING HUMAN HEART.

Amelia Focaccio, Patricia Larrabee, Mary M. Wollmering, Michael R. Bristow. University of Utah, Salt Lake City, Utah.

Xamoterol (X) is a ß-adrenoceptor partial agonist with an intrinsic activity of approximately 0.4 in model systems. X has been reported to improve left ventricular performance in patients with mild to moderate heart failure, but in severe heart failure (SHF) X has been associated with increased mortality. Since data on the hemodynamic effects of X in SHF are limited and since it has been proposed that X acts solely as a ß-blocking agent in SHF, we investigated the ß-agonistic activity of X in preparations derived from the hearts of patients with SHF. In crude myocardial membranes derived from 7 end-stage failing ventricles (receptor density = 28.3 fmol/mg, decreased by 68%) removed at the time of transplantation X competed with ^{125}[I]ICYP for two classes of binding sites. The K_H was 31.7 ± 11.5 nM and the K_L was 5847 ± 2041 nM, indicating 184 fold selctivity for $ß_1$ vs $ß_2$ receptors. At a dose range of 10^{-9} to 10^{-4} M X alone did not increase force of contraction in isolated right ventricular trabeculae (n=10), in agreement with a previous report. However, in the presence of a minimally effective dose of forskolin (ED_{20}) to augment adenylate cyclase catalytic activity, X induced a 1.7 fold increase in isometric systolic tension (p<.05) with an ED_{50} of 8.1 nM (n=15); the maximum response was 26.4% of that produced by the full agonist isoproterenol.
CONCLUSION: X can act as a $ß_1$ selective partial agonist in end-stage failing human heart.

HEMODYNAMIC RESPONSES TO INTRACORONARY INFUSION OF CALCITONIN GENE-RELATED PEPTIDE IN PATIENTS WITH CONGESTIVE HEART FAILURE

Jean Luc Dubois-Randé, Serge Adnot, Pascal Merlet, Christophe Benvenuti, Said Sediame , Alain Castaigne. Henri Mondor's Hospital, Creteil, 94010, FRANCE.

Calcitonin Gene-Related peptide (CGRP) has been shown to affect coronary vascular tone and cardiac function in experimental studies. We studied the hemodynamic responses to intracoronary infusion of CGRP in 9 patients with an idiopathic dilated cardiomyopathy (LVEF=21±8.5 %). Right (Swan-Ganz) and left catheterizations (Microtip Millar catheter) were performed to determine: CI: l.min-1.m-2; LVEDP: mmHg; peak positive LV dP/dt (mmHg.s-1); mean arterial pressure (MAP:mmHg) and systemic vascular resistance SVR: mmHg.min. l-1). Coronary sinus blood flow: ml.min-1 (Cq) was assessed by continuous thermodilution technique (Webster catheter) and coronary vascular resistance (CR) was then calculated (mmHg.min.ml-1). CGRP was infused into the left main coronary artery at incremental infusion rates of 15 (1), 50 (2), 150 (3) and 600 (4) pmol/min. Mean results are expressed on table. B= baseline; HR= heart rate: bpm; SO2= coronary sinus oxygen saturation(%)

*p<.05	HR	MAP	LVEDP	CI	SVR	+dP/dt	Cq	SO2	CR
B	87	87	18.3	2.1	36	710	107	26	0.78
1	87	88	18.7	2.15	36	709	114	27	0.75
2	85	88	18.3	2.14	35	714	118	29	0.76
3	92	80*	15*	2.67*	27*	729	124*	37*	0.60*
4	100*	72 *	1i*	3.1*	20*	788	134*	40*	0.53*

At the two intracoronary lowest doses of CGRP no systemic effect occurred and no effect on cardiac function and coronary hemodynamics were observed. The two highest doses induced systemic and coronary vasodilation but no change of peak positive LV dP/dt. These results suggest that CGRP has a role in the modulation of vascular tone but does not affect cardiac contractility.