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 B-blocker/vasodilator that is undergoing clinical trial for heart failure treatment. Data from animal screens suggest that C is a non-selective B-blocking agent with vasodilator properties due to a-blockade. Because of species differences in animals vs human adrenergic receptor pharmacology, we have characterized the B- and a-blocking activity of C in preparations derived from nonfailing (NF) and failing (F) human ventricles and compared the results to the selective B1, blocking agent mecoprolol (M) and the nonselective B-blocker/vasodilator bucindolol (B).

Results of radioligand-ligand competition curves (CRC) performed in crude myocardial membranes with and without 3x10\(^{-8}\)M Gpp(NH)p (G) were: (values \pm SEM)

<table>
<thead>
<tr>
<th>Group</th>
<th>CRC</th>
<th>agonist IC50 (nM)</th>
<th>B1 IC50 (nM)</th>
<th>B2 IC50 (nM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>M</td>
<td>40</td>
<td>40</td>
<td>&gt;100</td>
<td>&lt;10</td>
</tr>
<tr>
<td>B</td>
<td>10</td>
<td>10</td>
<td>&gt;100</td>
<td>&lt;10</td>
</tr>
<tr>
<td>C</td>
<td>2</td>
<td>2</td>
<td>&gt;100</td>
<td>&lt;10</td>
</tr>
</tbody>
</table>

Conclusions: 1) For C the B1 receptor affinity (Kb) is 2.5 times that of B2. The B1/B2 selectivity ratio is 5 times (M). 2) As does B, C exhibits an "agonist" binding site modulated by guanine nucleotides that does not confer drug inhibited CAMP PDE in a concentration-dependent manner.

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

Jean-Luc Dubois-Brezellec, Serge Adnot, Pascal Merlet, Christophe Benvenuti, Said Sedrane, Alain Castaigne, Henri Mondor's Hospital, Creil, 95010, 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 (LVF=31.2 \pm 8.5 %). Right (Swan-Ganz) and left catheterizations (Microtip Millar catheter) were performed to determine: CI, 1/min/m²; LVEDP, mmHg; peak positive LV dP/dt, mmHg/(s²); mean arterial pressure (MAP), mmHg; and systemic vascular resistance (SVR), mmHg/L/min. CGRP was infused into the left main coronary artery at incremental infusion rates of 15, 50, 150 and 600 (4) pmol/min. Mean results are expressed on table. B= baseline; HR= heart rate: bpm; SO2= coronary sinus oxygen saturation(%)

\[ \frac{pc.05}{HR} = MAP = LVEDP = CI = SVR = CR = mmHg/min/L/min.1] \]

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.