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Long-term benefits of the selective peripheral dopamine-ß-hydroxylase inhibitor BIA 5-453 in heart failure

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The present study examined the effects of BIA 5-453 ((R)-5-(2-aminoethyl)-1-(6,8-difluorochroman-3-yl)-1,3-dihydroimidazole-2-thione hydrochloride), a peripheral reversible dopamine-ß-hydroxylase (DβH) inhibitor (Beliaev A. et al., 2006) that decreases norepinephrine (NE) levels in sympathetically innervated tissues, on cardiac and systemic hemodynamics and cardiac remodeling in male cardiomyopathic hamsters (Bio TO-2 dilated strain).

The treatment with BIA 5-453 (3 mg/kg/day, p.o.) or enalapril (20 mg/kg/day, p.o.) was started at 120 days of age and the variables of interest were measured after 61-78 days of treatment. BIA 5-453 had no statistically significant effects (p>0.05) on mean, systolic and diastolic arterial blood pressure and heart rate as compared with vehicle control group. BIA 5-453 increased cardiac output (7.1 0.6 vs 5.7 0.7 ml/min) and stroke volume (0.038 0.003 vs 0.029 0.003 ml, p<0.05) as compared with vehicle. BIA 5-453 decreased the total peripheral resistance (7.8 0.7 vs 10.8 1.6 mmHg/min/ml, p<0.05). Enalapril significantly decreased mean, systolic and diastolic arterial blood pressure (p<0.001) and heart rate (p<0.05). Enalapril tended to slightly increase cardiac output (6.2 0.5 vs 5.7 0.7 ml/min) and stroke volume (0.034 0.002 ml vs 0.029 0.003 ml) as compared with vehicle. In contrast, it significantly decreased the total peripheral resistance as compared with vehicle (6.7 0.4 mmHg/min/ml vs 10.8 1.6 mmHg/min/ml, p<0.05). BIA 5-453 had no significant effects on left ventricle wall thickness, but decreased left ventricle collagen density (4.08 0.32% versus 5.25 0.44%, p<0.05). Enalapril had no significant effects on left ventricle wall thickness but decreased left ventricle collagen density (3.60 0.21% versus 5.25 0.44%, p<0.01). After 260 days, BIA 5-453 and enalapril increased survival as compared to vehicle. At 20% of survival in cardiomyopathic hamsters with advanced congestive heart failure the mean survival benefit of BIA 5-453 and enalapril was 31 and 42 days per animal.

It is concluded that in cardiomyopathic hamsters, BIA 5-453 improved systemic hemodynamics and prevented cardiac fibrosis. The hemodynamic and cardiac remodeling improvements with BIA 5-453 likely explain the increase in survival.