Haemodynamic response to converting enzyme inhibitor and Saralasin in salt-depleted dogs; relation to plasma renin activity

J. CONWAY, R. HATTON & J. KEDDIE

Biology Department, ICI Ltd, Pharmaceuticals Division, Alderley Park, Macclesfield, Cheshire, SK10 4TF

Interference with the renin-angiotensin system is known to result in a fall in blood pressure. The purpose of this study was to determine the level of plasma renin activity at which angiotensin may play a role in the control of blood pressure.

Male beagle dogs were chronically implanted with carotid artery and jugular vein vinyl catheters for measurement of blood pressure (BP), central venous pressure (CVP) and cardiac output (CO-dye dilution). Plasma renin activity (PRA) by radio-immunoassay was measured in arterial blood. The animals received a low sodium diet (5 mEq/day) for a period of 8 days; a diuretic was given on alternate days. Converting enzyme inhibitor (CEI, SQ 20881, 0.5 mg/kg i.v.) was administered to 6 dogs on days 2, 4, 6 and 8 whilst 4 dogs were similarly treated with Saralasin (Sar^1-ala^8-angiotensin II, S, 50 μg/kg i.v.). Haemodynamic measurements were made immediately prior to and after CEI or S treatment.

Sodium depletion by this procedure resulted in a gradual increase in PRA from approximately 1–30 ng $ml^{-1}h^{-1}$ with little overall change in BP. A progressive reduction in CO and CVP occurred with an elevation of calculated total peripheral resistance (TPR). Administration of CEI or S produced a fall in mean BP (Y) which was related to the initial PRA level (X).

For CEI $Y = -0.41 + 23.32 \log X$ ($r = 0.76$)

For S $Y = -18.33 + 29.30 \log X$ ($r = 0.75$)

For a given PRA value S was less effective than CEI in lowering BP and the level of PRA about which the fall became significant was 1.0 to 2.0 ng $ml^{-1}h^{-1}$ with CEI.

Table 1 shows that there was no clear relationship between the fall in BP and increase or decrease in heart rate (HR). A tachycardia was observed only during marked salt depletion (PRA > 20 ng $ml^{-1}h^{-1}$) but was inappropriate for the degree of BP fall. Likewise the fall in BP was accompanied by minimal change in CO. With both CEI and S the major determinant of BP fall was a reduction in TPR. As depletion was induced, TPR increased slowly and the inhibitors revealed that the component due to angiotensin was increased.

These results suggest that the renin-angiotensin system may play a role in control of BP in the dog at levels of PRA which are only slightly above normal values. The cardiac response to a fall in BP was impaired when the renin-angiotensin system was blocked.

Table 1 Haemodynamic response (mean ± s.e. mean) to converting enzyme inhibitor and Saralasin during salt-depletion in the dog.

	Converting-enzyme inhibitor (n = 6)				*Saralasin (n = 4)*			
	Day 0	*Day 8*			*Day 0*	*Day 8*		
Parameter	*Control*	*Pre*	*Post*		*Control*	*Pre*	*Post*	
PRA (ng $ml^{-1}h^{-1}$)	0.97 ± 0.25	27.04 ± 7.38			1.57 ± 0.21	29.90 ± 5.35		
BP (mm Hg)	107.5 ± 3.4	110.7 ± 3.4	75.3** ± 5.9		98.3 ± 3.1	103.8 ± 5.6	78.3** ± 1.7	
HR (bts/min)	80.7 ± 11.8	116.3 ± 8.4	137.2* ± 17.8		84.3 ± 4.3	102.5 ± 4.3	130.0* ± 10.0	
CO (l/min)	2.43 ± 0.24	2.00 ± 0.20	1.94 ± 0.29		2.81 ± 0.43	2.07 ± 0.35	2.21 ± 0.39	
TPR (Dyne sec/cm^5)	3715 ± 364	4635 ± 470	3337** ± 378		2967 ± 394	4267 ± 534	3109** ± 559	

* = $P<0.05$; ** = $P<0.01$. Differences from pre-dose value