D005
HEMODYNAMIC EFFECTS OF QUINAPRIL IN HYPERTENSION. N Kumar, NH McAuliffe. Institute of Stress Medicine, Whitty, Ontario, Canada.

12 newly-detected hypertensive patients were examined using impedance cardiography. Baseline measurements of systolic blood pressure (SBP), diastolic blood pressure (DBP), heart rate (HR), total systemic resistance (TSR), and an estimate of cardiac output (CO) were made in each of five different situations. Subjects were examined 1) standing, 2) sitting, 3) during a mental arithmetic challenge, 4) a video game, and 5) with one hand immersed in ice water.

After baseline measurements, each patient received 20 mg of quinapril od for three months. Then all the measurements were repeated.

In all five situations, SBP and DBP decreased significantly after treatment compared to pre-treatment values - just as expected for an effective antihypertensive agent. TSR decreased standing and during the mental arithmetic challenge. Trends towards decreased TSR with treatment in other categories were not statistically significant. No significant change in HR or CO was observed in any situation.

Key Words: quinapril, hemodynamics, cardiac output, total systemic resistance

D006
IN VIVO BLOCKADE OF ANGIOTENSIN I RECEPTOR BINDING IN RATS IN COMPARISON OF CANDESARTAN CILEXETIL WITH LOSARTAN.HE FEID, D.T. Gilmour, N. Lassiter, C.J. Johnston. Department of Medicine, University of Melbourne, Austin & Repatriation Medical Centre, Melbourne, AUSTRALIA.

Angiotensin II antagonists are a novel class of drugs for the treatment of hypertension. These agents interfere with the actions of angiotensin II by selectively blocking the angiotensin AT1 receptor subtype. Candesartan cilexetil (TCV 115) is a newly developed angiotensin AT1 receptor antagonist. Candesartan cilexetil is rapidly converted in vivo to the active compound candesartan (CV 11974). Although losartan, the first orally active angiotensin AT1 receptor antagonist, possesses antagonistic properties, most of its actions in vivo can be attributed to its active metabolite EXP 3174. The aim of the present study was to compare the in vivo effects of candesartan cilexetil with those of losartan on angiotensin receptor binding in the rat kidney following oral administration. Male Sprague-Dawley rats (250-300 g) were gavaged with either candesartan cilexetil or losartan in doses of 0.1, 0.3, 1, 3, 10, or 100 mg/kg or corresponding vehicle. Rats were subsequently killed at 0, 1, 2, 6 or 24 h after administration, trunk blood collected and the kidneys removed. The effects of candesartan cilexetil and losartan on angiotensin receptor binding were assessed by quantitative in vivo autoradiography using the radioligand [125I]angiotensin II. Angiotensin II receptor binding in the kidney was mainly due to AT1 receptors with high levels of binding confined to the inner stripe of the outer medulla and cortex. There was high punctate binding in the cortical regions consistent with binding to glomeruli. Candesartan cilexetil (0.1-30 mg/kg) inhibited angiotensin II receptor binding to all anatomical sites of the kidney in a dose-dependent manner. Losartan (0.1-30 mg/kg) also produced dose-dependent inhibition of angiotensin receptor binding but was 10-100 times less potent than candesartan cilexetil. Inhibition of angiotensin receptor binding was maximal 1 h after administration of candesartan cilexetil (10 mg/kg) but 2 h for losartan (10 mg/kg), with inhibition for both drugs persisting at 24 h. Candesartan cilexetil also increased plasma renin activity to a greater extent than losartan and at a lower dose level. The findings suggest that candesartan cilexetil in vivo is more potent than losartan in inhibiting AT1 receptor binding in the rat kidney. Thus, candesartan cilexetil is a potent and selective AT1 receptor antagonist that produces rapid, complete and sustained inhibition of angiotensin II receptor binding in the rat kidney.

Key Words: candesartan, losartan, angiotensin II antagonists, AT1 receptor

D007

Previous studies have demonstrated that losartan could block the receptor of thromboxane A2 (TXA2) on the vascular wall. The aim of present study was to assess the effect of losartan on human platelet activation. Platelets were obtained from 15 healthy men with ages between 26 and 40 years. Platelet activation was measured by the changes in the light transmission of platelets-rich plasma stimulated by the TXA2 analogue, U46619 (5x10^-7 M) or ADP (10^-6 M). U46619-stimulated platelet aggregation was significantly inhibited by losartan in a dose-response manner. Only a high dose of EXP 3174 (5x10^-7 M) had the same effect as the in vivo active metabolite of losartan, which was able to attenuate U46619-induced platelet aggregation. Captopril (5x10^-6 M), an angiotensin I-converting inhibitor failed to modify U46619-induced platelet aggregation. Furthermore, the binding of [3H]U46619 to platelets was competitively inhibited by losartan, whereas only a high dose of EXP 3174 (5x10^-7 M) reduced the binding of [3H]U46619 to platelets. The effect of losartan on platelet activation induced by ADP (10^-6 M), a platelet agonist partially dependent on TXA2, was also tested. Losartan reduced ADP-stimulated platelet aggregation. In conclusion, losartan decreased platelet aggregation by a TXA2-dependent mechanism. EXP 3174 showed a lower potency than losartan to reduce TXA2-platelet activation. Captopril and exogenous angiotensin II had no effect on platelet activation. These results suggest that losartan reduced TXA2-dependent platelet activation independently of Ang II involvement.

Key Words: Platelets, AT-1 receptors, thromboxane A2, ang I converting enzyme inhibitors

D008

A number of studies have demonstrated an abnormal regulation of myocardial cell growth in hypertensive animals. Recent studies have suggested that apoptosis can be induced in cardiomyocytes by a variety of insults which include pressure overload. In the present study we have analyzed the expression of the Bcl-2 protein (which protects from apoptosis) and Bax protein (which acts as apoptotic promoter) in the left ventricle of spontaneously hypertensive rats (SHR). 17-week-old Wistar Kyoto rats (WKY) and 17 week-old SHR were used. Compared with WKY, untreated SHR exhibited a significant increase in Bcl-2 expression and a reduced expression of Bax protein. The ratio Bcl-2/Bax in SHR was higher than in WKY and suggested an antiapoptotic state. However, the numbers of apoptotic cells in the left ventricle of SHR was greater than in WKY (17.3 ± 0.03 vs 9.2 ± 0.04 p<0.05). Treatment of SHR with doxazosin, a specific a1-adrenoceptor antagonist, reduced blood pressure, increased Bax protein expression and reduced Bcl-2 expression, resulting in a Bcl-2/Bax proapoptotic index. However, the percentage of apoptotic cells in the left ventricle of doxazosin-treated rats was diminished (12.4 ± 0.92). Interestingly, treatment of SHR with hydralazine reduced blood pressure to a similar extent as doxazosin and modified Bax expression but not Bcl-2 protein expression. In conclusion, the ratio of expression of Bcl-2/Bax proteins in SHR could be occurring as a compensatory mechanism to maintain cell survival. Treatment with doxazosin reduced the percentage of apoptotic cells in the left ventricle.

Bax protein expression seems to be regulated by changes in blood pressure while Bcl-2 expression was only modified by a, adrenoceptor antagonism.

Key Words: alpha-1 receptors, left ventricle hypertrophy, apoptosis, doxazosin, bcl-2.