P-354
EPIERENONE DOSE-RESPONSE RELATIONSHIP FOR ALDOSTERONE BLOCKADE

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Background: Eplerenone (EPL) is a selective aldosterone blocker approved at daily doses of 50-100 mg for the treatment of hypertension. EPL induces a resetting of the renin-angiotensin-aldosterone system, which is a reliable index of aldosterone blockade efficacy. This resetting reflects changes in sodium and potassium balance, which contributes to the beneficial effects of aldosterone blockade.

Methods: Three placebo-controlled, parallel group, dose-finding studies were evaluated to determine the magnitude of active and total renin (AR, TR) and aldosterone (SA) release in hypertensive patients treated with EPL 25-400 mg, total daily dose.

Results: A linear dose-dependent stimulation of AR, TR, and SA was observed. The slope of increase was greater for SA than for AR or TR, and was present in the absence of rise in serum potassium (SK+), below 400 mg daily. Blood pressure reductions were dose dependent, with no correlation with baseline AR, TR, or SA or their changes from baseline.

Conclusions: In essential hypertensive patients, a dose-dependent stimulation of AR, TR, and SA is observed with eplerenone, which, below 200 mg, remains within physiological values. Blood pressure falls were independent of renin and aldosterone levels.

Key Words: eplerenone, renin, aldosterone

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ANGIOTENSIN CONVERTING ENZYME INHIBITORS AND ALDOSTERONE RECEPTOR BLOCKERS IN HYPERTENSIVE AFRICAN AMERICANS

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Introduction: African-American hypertensives (AA) respond poorly to angiotensin converting enzyme inhibitors (ACEI) and angiotensin receptor blockers (ARB) individually. This study investigates the effect of ACEI and ARBs individually and in combination, on diastolic blood pressure (DBP), plasma renin activity (PRA) and aldosterone II levels, in these patients.

Methods: After baseline evaluation 44 AA patients, age 61.2±9.6 yrs, were randomized to ACEI enalapril (E) 10 mg (E4), increased to 20 mg (E8) after 4wks, or ARB candesartan (C) 16 mg (C4) increased to 32 mg (C8) after 4wks. After a total of 8wks of therapy, patients were crossed over to the other arm. Patients not responding to either of the two drugs were treated with a combination of both, starting with enalapril 10mg +candesartan 16 mg (CE4) for 4wks and then enalapril 20 mg +candesartan 32mg (CE8) for 4 wks. At the end of each phase complete clinical and laboratory evaluation including chemistry, PRA and aldosteron II levels, was done.

Results: At 4 8 wks DBP was significantly reduced with both E C. Non-responders (n=17) who received combination therapy with both E + C, showed only minimal additional fall in DBP. PRA increased only with C and CE at 4 8 wks. All levels increased only with high dose E.

Conclusion: All treatments decreased DBP significantly but the magnitude of change was small. The relatively poor response of BP to ACEI and ARBs in AA may be related to inadequate blockade of angiotensin converting enzyme or AT1 receptor or rapid return of ATII level to baseline. Combination of ARB and ACEI did improve the response significantly.

Key Words: Essential Hypertension, Angiotensin Receptor Blockers, African-Americans

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NOCTURNAL INAPPROPRIATE ALDOSTERONE ACTIVITY AND REDUCED POTASSIUM BALANCE IN SALT SENSITIVE HYPERTENSIVES WITH BLUNTING OF NIGHTTIME BP FALL


Salt sensitive hypertensives (SSHT) differently from salt-resistant −SR are prone to exhibit a blunted nocturnal BP fall when switching from low to high salt intake. In 10 black SSHTs (ageing 35-64 yrs, 5 male) and in 10 black SRs (ageing 32-60 yrs, 4 male) we examined separately during daytime (6:00-22:00 h) and nighttime (22:00-6:00h), the BP (Spacelabs 90207), the aldosterone activity by measuring plasmatic aldosterone to renin ratio (ARR), and the plasma and urinary sodium, potassium and creatinine values, on the last day of 2x2 weeks on high-sodium diet (HS, 300 mmol Na+/d) and on low salt diet (LS, 20 mmol Na+/d-2 weeks) and after an acute salt load while on LS diet (LS-infusion) (i.v. infusion

Key Words: Renin-Angiotensin System, Ductus Arteriosus, Coil closure...
of 2L NaCl both during daytime and nighttime). On LS, HS and LS-infusion, nighttime/daytime MAP fall (%) were in HTSS of 9.4(1.1) on LS-pl; 3.4(0.9) on HS-pl; and 2.4(1.0) on LS-infusion (p<0.03, LS v HS LS-infusion) and in SR of 9.2(1.2) on LS-pl; 7.4(1.3) on HS-pl; and 6.8(1.2) on LS-infusion (n.s.). On HS, ARR was 1.8 times greater in SSHT vs SR and it was attenuated from daytime to nighttime by 25.6 (6.3)% (p<0.02) in SRs subjects but only by 5.1 (1.1)% (n.s.) in SSHT; saline infusion on LS reduced ARR during nighttime by 37.4 (7.4) % (p<0.02) in SR subjects but only by 1.1 (1.9) % (n.s) in SSHTs. Also on LS, saline infusion similarly increased sodium excretion in both SR and SSHT but it decreased serum potassium and reduced urinary potassium excretion (from daytime to nighttime) in SR whereas the opposite occurred in HTSS. We conclude that differently from SR, SSHT while submitted to chronic or acute sodium loading show greater BP levels during nighttime which may be related with a nocturnal inappropriate increase of aldosterone activity and with a reduced potassium balance.

Key Words: Salt sensitive hypertension, Renin angiotensin system, Mechanisms

P-357
NON-ACE PATHWAY IN RENAL ANGII
GENERATION: ARE THERE ETHNIC DIFFERENCES?
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We have recently reported evidence to indicate that AngII-dependent renal vascular tone differs in healthy blacks and whites. There is evidence for AngII generation via pathways that do not involve ACE in humans. In view of the risk of nephropathy in blacks and the role that AngII plays for AngII generation via pathways that do not involve ACE in humans. We have recently reported evidence to indicate that AngII-dependent renal vascular response to captopril and 16 mg candesartan on separate days. The groups had both similar baseline RPF on the captopril day (549 ± 26 vs 561 ± 28 ml/min/1.73m²; blacks vs whites) and comparable increases with captopril 610 ± 29 (p = 0.0009) vs 628 ± 44 ml/min/1.73m² (p = 0.0069); blacks vs whites. On the captopril day, baseline renal plasma flow response (PAH clearance) was measured in subjects who randomly received 25 mg captopril and 16 mg candesartan on separate days. The change in the RPF response from baseline with captopril in blacks was 60 ± 12 ml/min/1.73m² compared to 99 ± 14 ml/min/1.73m² with candesartan (p = 0.0598). For whites the response was 67 ± 20 ml/min/1.73m² with captopril and 111 ± 24 ml/min/1.73m² with candesartan (p = 0.008).

The renal vascular response to candesartan was about 40-50% larger than the renal vascular response to captopril. Thus, a significant non-ACE pathway for AngII generation exists in both groups and does not appear to differ quantitatively in blacks.

<table>
<thead>
<tr>
<th>Captopril</th>
<th>Captopril</th>
<th>Candesartan</th>
<th>Candesartan</th>
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<tbody>
<tr>
<td>Basal</td>
<td>Response</td>
<td>Delta</td>
<td>Basal</td>
</tr>
<tr>
<td>Black</td>
<td>549 ± 26</td>
<td>610 ± 29</td>
<td>60 ± 12</td>
</tr>
<tr>
<td>White</td>
<td>561 ± 28</td>
<td>628 ± 44</td>
<td>67 ± 20</td>
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</tbody>
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Key Words: race, kidney, non-ACE pathway

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RENIN-ANGIOTENSIN SYSTEM ALTERS NKCC-1 COTRANSPORT ACTIVITY IN HEALTHY WHITE BUT NOT BLACK SUBJECTS
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African Americans have been shown to exhibit lower urinary potassium excretion when compared to Caucasians. Angiotensin II regulates both potassium handling by the kidney and the Na-K-2Cl (NKCC) cotransporter in vitro. However, little is known about the role of the renin-angiotensin system (RAS) in human NKCC cotransport regulation in vivo. We hypothesized that regulation of RAS would induce concomitant alterations in NKCC activity in humans. The kidneys and erythrocytes express NKCC-1 isoform. Therefore, we measured NKCC-1 activity in freshly isolated ex vivo red cells from 12 healthy blacks and 11 healthy whites in high (200 mmol/d) and low (10 mmol/d) salt balance, followed by a measure 24 h-post candesartan [16 mg] to block angiotensin II type 1 receptors on low salt diet. Baseline NKCC cotransport activity was significantly lower in Blacks when compared to Whites in balance on a typical high salt diet, and was reduced when the subjects were placed on a low salt diet in whites only. Administration of candesartan reversed the reduction seen with low salt diet in whites, where as in blacks there was no significant effect. These data suggest altered in vivo regulation of NKCC-1 via RAS in Blacks when compared to Whites, and provide a mechanism that may in part explain the altered potassium handling observed among otherwise healthy African Americans.

<table>
<thead>
<tr>
<th></th>
<th>High Salt</th>
<th>Low Salt</th>
<th>Low Salt + Candesartan</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blacks</td>
<td>0.37 ± 0.7</td>
<td>0.51 ± 0.12</td>
<td>0.43 ± 0.07</td>
</tr>
<tr>
<td>Whites</td>
<td>0.85 ± 0.16*</td>
<td>0.64 ± 0.10</td>
<td>0.76 ± 0.09##</td>
</tr>
</tbody>
</table>

Mean ± SE, mmol/L cells × h; (*) LS vs HS P < 0.04; (##) LS vs LS + candesartan P < 0.03

Key Words: ion transport, angiotensin receptor blockade, nkcc

P-359
CONN’S SYNDROME CAUSED BY ALDOSTERONE-PRODUCING ADRENOCORTICAL CARCINOMA:
REPORT OF TWO DIVERGENT CASES AND A META-
ANALYSIS OF ALL REPORTED CASES SINCE 1955
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Aldosterone-producing adrenocortical carcinoma (APAC) is a rare disorder; hence, as a result of the paucity of information on its biological behaviour, the diagnosis is often delayed. To date, no data on survival rates and diagnostic markers signs of malignancy is available.

To report on two cases that featured an unusual course and to delineate the clinical characteristics and natural history of APAC based on a meta-analysis of all reported cases from the literature since 1955. A database was created with all available information on demography, imaging results, hormonal data, gross features, histology, and clinical course. We used Kaplan Meier and Cox regression analysis to calculate survival curves and recurrence-free survival, and to identify the impact of several covariates on survival.

We identified in the literature 62 cases of APAC, including the present two, all presenting the classical signs of Conn’s syndrome. Plasma