INTRA-INDIVIDUAL RESPONSES TO BLOCKADE OF THE RENIN-ANGIOTENSIN SYSTEM BY AN ACE INHIBITOR (LISINOPRIL) & AN ANGIOTENSIN RECEPTOR ANTAGONIST (CANDESARTAN)

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Angiotensin receptor antagonists (AT1A) are recommended for hypertensive patients in whom angiotensin converting enzyme inhibitors (ACEI) are effective but poorly tolerated. No study has, however, systematically evaluated within subject responses to these two classes of drugs. The current study was a randomised, double blind crossover study of the ACE inhibitor, lisinopril, and the AT1A, candesartan, with the primary efficacy parameter being the comparison of intra-individual response rates, where a “responder” was defined as a patient with a mean sitting diastolic blood pressure reduction >10 mmHg and/or mean diastolic blood pressure <90 mmHg. Assuming a difference in “response” proportions of 22% and a proportion of discordant pairs of 50% with α = 0.05 and β = 0.20, 76 pairs were required to complete the evaluation on the two treatments. Following a washout period of four weeks, 92 patients were randomised to one of the two drugs. If after two weeks the goal of therapy had not been achieved (diastolic blood pressure <90 mmHg) the initial dose of lisinopril (10 mg) or candesartan (8 mg) was increased to 20 mg or 16 mg respectively. Blood pressures were recorded at six weeks and following a second washout period of two weeks, the patients were crossed over to the alternate regimen for a further six weeks. 82 patients completed both limbs of the trial. Mean blood pressure falls after six weeks treatment were similar for the two drugs (candesartan systolic bpd =14.0 ± 12.6 mmHg; lisinopril =15.8 ± 12.8 mmHg; diastolic bp (candesartan =−9.6 ± 8.4 mmHg; lisinopril =−10.6 ± 7.6 mmHg). There was marked heterogeneity in blood pressure responses to the two treatments. 51% of patients responded to both drugs; 16% were non-responders to both drugs; 18% responded to lisinopril but not candesartan and 15% responded to candesartan but not lisinopril. There was no statistical difference between the two treatments for the analysis of discordant pairs (p = 0.56). Conclusion. In approximately one in six cases, responsiveness to blockade of the renin-angiotensin system by either an ACEI or an AT1A fails to predict responsiveness to blockade by the alternative class of drug. Phenotypic markers, including renin status, and genetic polymorphisms of the renin-angiotensin system are being evaluated for potential determinants of responsiveness to these two classes of agents.

Key Words: ACE inhibitor; angiotensin antagonist; crossover trial

ANGIOTENSIN-(1–7) AND VASOPEPTIDASE INHIBITION


The contribution of angiotensin-(1–7) to the antihypertensive actions of omapatrilat (OMA), a novel vasoconstrictor inhibitor, was evaluated in 15 salt-sensitive, low renin, hypertensive subjects as a sub-study of a multi-center randomized, double-blind, parallel study of 4 wks duration. As illustrated in the Figure, OMA (40 mg) caused statistically significant rises in the urinary excretion of both Ang-(1–7) (upper panel) and atrial natriuretic peptide (ANP, middle panel) throughout the dosing period at day 28 of treatment (–After). The effects of OMA on Ang-(1–7) and ANP excretion were associated with a sustained control of blood pressure as denoted by the differences in the 24 hr ambulatory systolic blood pressure measurements at days 0 (SBP, before) and 28 of treatment (SBP, After).

A single molecule inhibiting neutral endopeptidase and angiotensin converting enzyme effectively controlled salt-sensitive hypertension by a mechanism related to inhibition of NEP 24.11 for which Ang-(1–7) is a substrate. These data are the first to show a role of Ang-(1–7) to the antihypertensive renal response of a novel vasoconstrictor inhibitor in the treatment of essential hypertension.

Key Words: Ang-(1–7); omapatrilat; atrial natriuretic peptides; hypertension