IRBESARTAN RESULTS IN MORE COMPLETE BLOCKADE OF HUMAN RENAL AT1-RECEPTOR MEDIATED EFFECTS THAN DOES CANDESARTAN CILEXETIL AS EVIDENCED BY HIGHER PLASMA RENIN LEVELS

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Objective: It is known that the angiotensin II AT1 receptor antagonists block the renin angiotensin system and result in consequent increases in plasma renin levels by interfering with feedback. Further, it has previously been documented that irbesartan (IRB) and candesartan cilexetil (CAN) exhibit a longer duration of angiotensin II (ANG II) antagonism than do losartan and valsartan (Malerczyk C et al.: Br J Clin Pharmacol 1998;45:567–573; Belz GG et al.: Clin Pharmacol Ther 1999;66:367–373). We evaluated data from a direct comparison of the ANG II antagonistic effects of IRB and CAN to evaluate their effects on stimulating plasma renin levels.

Methods: Eighteen healthy males were enrolled in a double-blind, randomized, cross-over study and received IRB 150 mg and CAN 8 mg for one week each. Plasma renin activity at rest and the rightward shift (measured as dose-ratio [DR-1]) of blood pressure response curves to exogenous ANG II were used to assess the ANG II antagonism in vivo. The degree of receptor occupation in plasma ex vivo was determined by radioligand rat lung receptor assay (RRA).

Results: Both IRB and CAN shifted ANG II dose effect curves rightward to a similar degree (max ∼35-fold) and yielded mean DR-1s of >1 for approximately 48 hours, indicating strong and long lasting ANG II antagonism. The antagonistic activity in plasma as measured by RRA was distinctly higher (p < 0.01) following administration of IRB. Plasma renin activity during the periods with high antagonistic activity was significantly higher following IRB (p = 0.02) in absolute terms (left figure) and when related to the ANG II antagonistic effect (right figure).

Conclusion: The distinctly higher antagonistic plasma activity following IRB as compared with CAN is associated with stronger renal antagonistic effects as demonstrated by greater plasma renin activity. This superiority of IRB on tissue AT1 receptors may have significant clinical implications.

Key Words: Irbesartan; candesartan; AT1 receptor antagonists; renin angiotensin system

IRBESARTAN RESULTS IN SUPERIOR BLOOD PRESSURE REDUCTION VS VALSARTAN

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Objective: Evidence has been obtained that irbesartan (IRB) provides a greater blood pressure reduction as compared with the highest labeled dose of losartan (LOS) (Kassler-Taub et al., Am J Hypertens 1998;11:445–453; Oparil et al., Clin Ther 1998;20:398–409). It has also been shown that IRB may provide superior blockade of angiotensin II (ANG II) as compared with LOS and valsartan (VAL) (Belz et al., Clin Pharmacol Ther 1999;66:367–373; Mazzolai et al., Hypertension 1999;33:850 – 855). The aim of this study was to determine if the superior blockade of ANG II with IRB as compared with VAL translated into greater antihypertensive efficacy.

Methods: Mostly male (65%), Caucasian (96%) subjects with a mean age of 55 years were randomized to IRB 150 mg (n = 211) or VAL 80 mg (n = 215) in an 8-week, double-blind study. Subjects had mild-to-moderate hypertension (mean baseline trough ambulatory blood pressure 148/94 and 150/96 mm Hg and mean baseline 24-hour ambulatory blood pressure 142/88 and 144/89 mm Hg in the IRB and VAL groups, respectively). The primary outcome measure was change in mean trough (24th-hour post-dose) ambulatory diastolic blood pressure (ADBP).

Results: IRB reduced trough ADBP at week 8 by 1.89 mm Hg more than did VAL (–6.7 vs –4.8 mm Hg, respectively; p = 0.035). Similarly, IRB produced a 4.1 mm Hg greater reduction in trough ambulatory systolic blood pressure (ASBP) than did VAL (–11.6 vs –7.5 mm Hg, respectively; p < 0.01) (see left figure). Statistically significant reductions in favor of IRB vs VAL were also observed for mean 24-hour systolic and diastolic blood pressures (–10.2/–6.4 vs –7.8/–4.8 mm Hg, respectively) (see right figure), for office trough systolic and diastolic blood pressures, and for percent of patients who attained blood pressure normalization (52.5% vs 38.2%, respectively; p = 0.004) or response (63.9% vs 44.3%, respectively; p < 0.0001).

Conclusions: IRB results in statistically superior blood pressure reduction and control rates as compared to VAL. These results are analogous to those obtained in comparisons of IRB and LOS, and may be due to the significantly greater antagonism of ANG II previously demonstrated with IRB as compared with VAL and LOS.
Key Words: Arterial hypertension; meteorological factors; teorologically-dependent patients.

**A108**

**CLIMATIC AND METEOREOLOGICAL REGULARITIES OF THE INDICES OF 24-HOURS BLOOD PRESSURE MONITORING AND ANTIHYPERTENSIVE EFFECT OF AMLODIPINE IN PATIENTS WITH ESSENTIAL HYPERTENSION**

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Climatic and meteorological conditions are one of the factors essentially effecting not only the frequency of cardiovascular catastrophies but determining arterial hypertension course in general. In order to study blood pressure (BP) profiles depending on climatic and meteorological conditions we made a comparative analyses of the 24-hours monitoring of BP and climatic and meteorological characteristics. We compared the levels and variability of arterial BP, an increase of BP in the morning and a decrease at night with hourly indices of the speed of the wind, atmospheric pressure, cloudiness, dampness, meteorological phenomena and the weather type. We also have studied the effect of amlodipine on 24-hour BP. Ceteris paribus it was found that the percent time elevation according to the systolic and diastolic BP are the lowest in the 1st weather type and constitute 32.1 ± 1.3% and 18.5 ± 0.9%, respectively. In the 2nd and 3rd types it increases according to the systolic BP to 42.3 ± 2.0% and 56.3 ± 2.1% and the diastolic arterial pressure up to 48.3 ± 2.1% and 64.3 ± 2.8%. A greater increase in the diastolic BP demands searching for the drugs to overcome non-stability of the diastolic BP. After 3 weeks of treatment amlodipine produced a significant increase both systolic and diastolic BP from 164.38 ± 1.21 to 139.47 ± 1.04 mm Hg and from 99.50 ± 1.06 to 87.41 ± 0.97 mm Hg, respectively (p < 0.001 for both). The percent mean change of systolic and diastolic BP from baseline for daytime BP was also greater with amlodipine at week 3. The most critical meteorological characteristics were the wind speed and formation of extraordinary meteorological phenomena. It was in these conditions that non-stability of arterial pressure was significant. Amlodipine provides adequate antihypertensive coverage in meteorologically-dependent patients.

Key Words: Arterial hypertension; meteorological factors; amlodipine

**A109**

**THE IMPORTANCE OF ACE IN CORONARY CIRCULATION AND THE EFFECT OF ACE INHIBITION BY RAMIPRILAT IN THE ISOLATED PERFUSED RAT HEART**


Angiotensin I (AngI) can be converted to Angiotensin II (AngII) by different enzymes including ACE and Chymase. In the coronary circulation Chymase has been described as the main pathway. We assessed the importance of ACE in coronary circulation by evaluating the vascular response to AngI in the isolated perfused heart of normotensive and hypertensive rats. Four experimental groups (n = 3–4) were included: normal Wistar rats weighting 200 to 400 g, surgically hypertensive rats due to aortic coarctation; normal rats treated with Ramipril (1 mg/kg/day PO) for 7 days and hypertensive rats treated the same way. Increasing concentration of AngII (1, 2, 8 ng) generated a dose dependent increase in coronary perfusion pressure (CPP) of 7.75 ± 0.25 mmHg, 36.5 ± 0.96 mmHg, 49.63 ± 2.98 mmHg in control rats and of 11.88 ± 1.88 mmHg, 47.13 ± 3.69 mmHg, 65.63 ± 3.29 mmHg in hypertensive rats. When we stimulated the heart with AngI (2 ng) the increment in CPP was higher in the hypertensive group compared to controls (30.75 ± 1.49 mmHg vs 22.88 ± 1.81 mmHg; p < 0.05). Changes due to AngI were more evident when control or hypertensive rats were treated with Ramipril for 7 days and then treatment was suspended. Under these conditions AngI increased CPP by 32.38 ± 2.48 mmHg and 55.25 ± 5.92 mmHg in control and hypertensive rats respectively. During in vitro perfusion with Ramiprilat (1 μM) we observed that the AngI induced increase in CPP was inhibited 78.15% in control rats, 81.69% in hypertensive rats, 51.73% in control rats treated for 7 days and 59.58% in hypertensive rats treated the same way. Moreover, inhibition of the AngI induced vasoconstriction by in vitro Ramiprilat was significantly reduced by coincubation with HOE140 (100 nM). Thus the present study suggests that AngI induced vasoconstriction in the heart is ACE dependent and that the enzyme’s expression is favored during the development of hypertension or treatment with systemic Ramiprilat. Furthermore we demonstrated that Ramiprilat’s effect depends on Bradykinin activity.

Key Words: Angiotensin; coronary circulation; ACE