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VERY-LOW-DOSE PERINDOPRIL 2 MG/INDAPAMIDE 0.625 MG COMBINATION GIVES HIGHER RESPONSE AND NORMALIZATION RATES THAN LOSARTAN 50 MG IN THE TREATMENT OF ESSENTIAL HYPERTENSION

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Objective: To compare the efficacy and tolerability of the very-low-dose perindopril 2 mg/indapamide 0.625 mg (P/I) combination with the angiotensin II antagonist losartan 50 mg (L50) in the treatment of essential hypertension.
Design and methods: This was a randomized, double-blind, parallel-group study. After a 2-week placebo period, all patients included were randomized to receive either P/I or L50 for a period of 12 weeks. Patients were 18 years of age or older and required a causal measurement of supine systolic blood pressure (sSBP) between 160 and 209 mm Hg and/or supine diastolic blood pressure (sDBP) between 95 and 114 mm Hg to be enrolled in the study. A 24-h ABPM (4 measurements per hour) was performed at week 0 and week 12.
Statistical analyses: To demonstrate the non inferiority of the P/I combination on causal BP measurement (sSBP and/or sDBP), minimal equivalence was tested using a one-sided test procedure with a value of $P < 0.025$ (per-protocol analysis). Responder and normalization rates in the two groups were compared by a chi^2 test and ABPM data by a Student *t* test. Safety data were analyzed on all randomized patients. A value of $P < 0.05$ was considered significant.
Results: Among the 277 patients randomized, 232 took part in per-protocol analysis (122 P/I; 110 L50). Demographic, clinical, and laboratory characteristics were comparable between the two groups at inclusion. Blood-pressure-lowering effects (casual measurement) were equivalent in the two treatment groups. The average decreases in sSBP were 21.9 ± 13.3 mm Hg for P/I and 19.8 ± 16.1 mm Hg for L50 (CI: -5.95, $+\infty$) (non inferiority $P = 0.0001$), and in sDBP were 14.8 ± 8.5 mm Hg for P/I and 12.9 ± 8.6 mm Hg for L50 (CI: -4.07; $+\infty$) (non inferiority $P = 0.029$). Responder rate (BP < 140/90 mm Hg and/or a decrease in sDBP ≥10 mm Hg and/or a decrease in sSBP ≥20 mm Hg) was significantly higher in the P/I group (91.0%) than in the L50 group (81.8%), with $P = 0.04$. Normalization rate (sDBP < 90 mm Hg) was also significantly in favor of the P/I group (75.4% [P/I] versus 60.0% [L50], $P = 0.012$). The average nighttime SBP decrease (ABPM) analyzed in 137 patients (74 P/I and 63 L50) was significantly greater in the P/I group (-10.8 ± 10.8 mm Hg [P/I] versus -7.5 ± 11.7 mm Hg [L50], $P = 0.045$). The rate of patients with at least one emergent adverse event was similar in the two groups. Emergent adverse events related to treatment (with a frequency >0.7%) corresponding to one patient per group only included cough (4.1% in P/I), dizziness/giddiness (1.5% in L50), and asthenia (1.4% in P/I and 1.5% in L50).
Conclusion: The very-low-dose perindopril 2 mg/indapamide 0.625 mg combination gives higher response and normalization rates than losartan 50 mg. This very-low-dose combination also provides a higher nocturnal decline in SBP (ABPM), which is a major significant predictor of cardiovascular complications. Both treatments were confirmed to have good and comparable tolerability.

Key Words: Fixed low dose combination; perindopril; indapamide; losartan; hypertension

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EFFECT OF LOW DOSE COMBINATION OF PERINDOPRIL AND INDAPAMIDE (PRETERAX) ON THE CORONARY MICROCIRCULATION OF RENOVASCULAR HYPERTENSIVE RATS

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The development of hypertension is accompanied by rarefaction of arterioles and capillaries in both animal models and humans. We report a series of experiments performed in rats with renovascular hypertension induced by unilateral nephrectomy and renal artery stenosis (Goldblatt 1K-IC). Animals were treated for 4 weeks, after renal artery clipping, either with an ACE inhibitor (perindopril 0.76 mg/kg/day), or with an indol derivative diuretic (indapamide 0.24 mg/kg/day) or with the combination of both drugs at the same doses as during monotherapy. Coronary microvessel densities (arterioles and capillaries) were evaluated by double immunolabelling and quantitative sterology in the left ventricular inner myocardium.

After 4 weeks of hypertension (MAP = 174 ± 11 vs. 124 ± 5 mmHg in normotensive controls, $P < 0.01$), *cardiac hypertrophy* (+59%, $P < 0.001$) was associated with a significant increase in myocardial arteriolar density (+27%, $P < 0.01$) and a decrease in capillary density (-12%, $P < 0.05$).

Treatment with perindopril prevented the increase in arterial pressure, heart weight and arteriolar density but did not significantly affect the low coronary capillary density in comparison with that measured in untreated hypertensive rats.

Treatment with indapamide preserved normal capillary myocardial density but did not significantly lower the blood pressure (169 ± 9 mmHg) and only slightly reduced the cardiac ventricular hypertrophy: -14% vs. untreated hypertensives ($P < 0.05$) and +37% vs. normotensives ($P < 0.01$). The combination of both drugs, perindopril and indapamide resulted in normal levels of arterial pressure and complete normalization of cardiac hypertrophy and arteriolar and capillary myocardial densities.
Conclusion: Blockade of the renin-angiotensin system by perindopril could inhibit large vessel growth but minimally affects the capillary density despite complete normalization of blood pressure. Indapamide could have beneficial effect on myocardial capillary density. The combination of indapamide and perindopril has additional effects and prevented the increase in blood pressure and cardiac weight, and reversed microvascular abnormalities.

Key Words: Microcirculation; rarefaction of coronary vessels