We found with Diltiazem a close correlation between the SBP values and the SBP decrease with a correlation coefficient = 0.6 and a 2-tailed $p < 0.0001$ (Pearson's correlation).

Diltiazem 180 mg in slow release capsules has a proportional effect on blood pressure evaluated by 24 hour ABPM: it produces a proportional decrease in the elevated blood pressure without inducing hypotension when patients present normal or low blood pressure values.

Key Words: Ambulatory BP Monitoring, Proportionality, Diltiazem

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TREATMENT OF ISOLATED SYSTOLIC HYPERTENSION IN A COMPARATIVE STUDY OF FOUR ANTIHYPERTENSIVE DRUGS

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To perform a comparative study of monotherapy or, if necessary, combination treatment for isolated systolic hypertension (ISH) with a diuretic, b-blocker, ACE inhibitor and calcium antagonist, we have studied in this non-blind, randomized study with four parallel treatment groups in outpatients hypertensives recruited from our antihypertensive clinic from January 96 to December 99. Patients after a 2-week washout period received 2.5/25 to 5/50 mg amiloride/chlorthalidone, 50 to 100 mg atenolol, 2-4 mg perindopril, or 5 to 10 mg felodipine, daily in the morning. Random measurements of resting blood pressure was used to monitor therapy and was performed 22 to 24 hours after taking the medication and every 4 weeks for 3 months. The aim of the treatment was to achieve an SBP <140 mmHg. If this was not reached after 4 weeks of monotherapy, then dual therapy was given with a combination of the study drugs. Triple therapy was instituted after a further 4 weeks, if required.The study included 1375 patients with essential hypertension, 106 (7.7%) of them found with ISH (systolic blood pressure SBP>/= 140 mmHg, diastolic blood pressure <90 mm Hg), 40 of which were males (37%). The mean age was 62.9 years and the body mass index 28.7 kg/m2. The four groups were consisted of about 25 patients with comparable basic characteristics. Only 96 patients, seventy of them (66%) over 60 years old completed the study, because 10 of them dropped out (2 with cough and 8 with peripheral edema). The antihypertensive effect of each drug, after 4 weeks of monotherapy was comparable and significant (mean SBP/DBP: felt from 160.6/81.5 to 143.2/74.4 mmHg, p<0 .001). The target SBP (SBP<140 mmHg) with monotherapy achieved 70 (73%) patients, 22 (88%) on felodipine, 15 (65%) on atenolol, 18 (75%) on amiloride/chlorthalidone and 15 patients (62%) on perindopril. Seventeen patients (27%) required dual therapy, and 9 (9.3%) needed triple therapy.

In descending order, the dihydropyridine calcium antagonist felodipine, the diuretic amiloride/chlorthalidone, the b-blocker atenolol and the ACE inhibitor perindopril, as single and combination therapy proved suitable for reducing blood pressure effectively for 24 hours in ISH, and were well tolerated.

Key Words: Antihypertensive drugs, Treatment, Isolated Systolic Hypertension

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BETA-BLOCKADE WITH NEBIVOLOL ENHANCES THE ACETYLCHOLINE-INDUCED VASODILATION IN THE CUTANEAOUS VASCULAR BED OF NORMOTENSIVE VOLUNTEERS

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This study was undertaken to assess whether the beta1-adrenoceptor blocker nebivolol(N) increases the vasodilatory response to acetylcholine(Ach) when administered orally to healthy subjects. To this end 12 volunteers were randomly allocated to a 8-day treatment with nebivolol (n), 5 mg once a day, and atenolol(A),50 mg once a day, according to a cross-over design, with a 1 week wash-out period between the two treatment phases. The forearm skin blood flow(SBF) response to Ach applied by iontophoresis was determined using a laser-Doppler scanner imaging system before(T0) and 3 hours(T3) after N or A dosing, both on the first (Day 1) and the last day (Day 8) of treatment. The following Table shows the responses of SBF (perfusion units) (means±SD; *p<0.05 versus T0):

	Day 1		Day 8	
	T0	T3	T0	T3
Nebivolol	98±93	441±109*	393±110	426±105*
Atenolol	396±97	410±99	380±109	394±98

Iontophoresis of 0.09% NaCl had no effect on SBF. These data indicate that nebivolol (administered at a dose commonly used in clinical practice), but not atenolol, enhances in humans the vasorelaxant activity of Ach in the skin vascular bed, which is compatible with a facilitation by this beta-blocker of the endothelium-dependent vasodilation.

Key Words: Beta-adrenoceptor blockade, Endothelial function, Skin microcirculation

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THE S-NITROSO DERIVATIVE OF OMAPATRILAT (VANLEV) CAN ACT AS A SUBSTRATE FOR CELL SURFACE PROTEIN DISULFIDE ISOMERASE AND THUS DELIVER NO TO THE CYTOSOL OF HUMAN UMBILICAL ENDOTHELIAL CELLS,IN VITRO

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Background: Omapatrilat (Vanlev) is a new vasopeptidase inhibitor. It simultaneously inhibits two key enzymes involved in the regulation of cardiovascular function, neutral endopeptidase and angiotensin-converting enzyme. Omapatrilat contains a free thiol group that can potentially act as a nitric oxide (NO)-carrier. In this study, we explored the ability Omapatrilat-NO to donate NO to the cytosol of by acting as a substrate for the enzyme cell-surface protein disufide isomerase.

Methods: These dynamic microscopy studies, were conducted on live human umbilical vein endothelial cells in vitro, with the aid of fluorescent intracellular NO-probe dansylhomocysteine. With this compound the kinetics of cell-surface protein disulfide isomerase-catalyzed NO transfer from S-nitrosothiols, like Omapatrrilat-NO can be directly evaluated. The levels of cell-surface protein disulfide isomerase protein, were also monitored as a function of Omapatrilat by Western blotting.

Results: The estimated KM of cell-surface protein disulfide isomerase for Omapatrilat-NO, in the presence of 10 micromolar Omapatrilat was 40 micromolar. When the kinetics were repeated after a 24 h pretreatment of the cells with 10 micromolar Omapatrilat, the KM decreased by 30-fold to 1.4 micromolar. Western blot analysis of secreted protein disulfide isomerase, indicated that the amount of protein also increased by nearly 5-fold upon a 24h incubation with Omapatrilat.

Conclusion: These studies show that the NO derivative of Omapatrilat is stable and can donate its NO to the cytosol through the action of the enzyme cell-surface protein disufide isomerase. These studies also demonstrate that Omapatrilat can affect the affinity of the enzyme as well as upregulating its excreteion by and unknown mechanism. The results presented here indicate that apart from vasopeptidase inhibiton, Omapatrilat could potentially act as a vasodilator by its ability to carry NO and to positively affect the enzyme resposible for the release of S-nitrosothiol-bound NO into the cells comprizing the vasculature.

Key Words: S-Nitroso derivative of omapatrilat, Endothelial NO-metabolism, Cell surface protein-disufide isomerase