C25

KININ DOES NOT CONTRIBUTE TO THE IMPROVEMENT OF INSULIN SENSITIVITY IN DELAPRIL TREATED FRUCTOSE FED RATS.

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[Purpose] We examined if kinin contributed to the improvement of insulin sensitivity by ACEI delapril. [Materials & Methods] Study 1: Male S-D rats were fed with fructose rich chow for 4 weeks. From the third week, delapril (10 mg/kg, D; n=8) or the angiotensin II receptor antagonist (AII-A) TCV-116 (1mg/kg, T; n=13) was administered by gavage once daily. Nine rats were treated with vehicle (V). Study 2: Minipumps containing either the bradykinin receptor antagonist Hoe140 (0.5mg/kg /day,D+H; n=8) or 0.9%NaCl (D+V; n=8) were placed subcutaneously on the day delapril was started. Steady state plasma glucose (SSPG): Insulin and glucose (2.5mU & 8mg/kg/min) were infused in the conscious state to measure the SSPG. [Results] Study 1: Mean blood pressure and SSPG were significantly lower in both D and T than V (106±8 & 110±4 vs 120±3 mmHg; and 171±4 & 171±7 vs 207±6 mg/dl). Study 2: There was no significant difference in SSPG between D+H and D+V (152±7 vs 191±17 mg/dl). [Conclusion] Both ACEI and AII-A improved insulin sensitivity in fructose fed rats and Hoe140 did not affect SSPG in ACEI treatment, suggesting that kinin did not contribute to the improvement of insulin sensitivity by ACEI.

Key Words:
kinin, ACE inhibitor, rat, insulin resistance

C26

BIOEQUIVALENCE STUDY OF COMBINATION OF INDAPAMIDE AND PERINDOPRIL ADMINISTERED AS ONCE TABLET OR TWO CAPSULES AFTER ORAL SINGLE DOSE.

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Combination of Angiotensin Converting Enzyme Inhibitors and diuretics is a potent treatment of hypertension. The aim of this study was to demonstrate the bioequivalence of the combination of Perindopril (Per : 4 mg) and Indapamide (Ind : 1.25 mg) administered orally as a single tablet or as two capsules each containing one of the components.Eighteen healthy male volunteers (20-26 years old) were included, they received either Per (4 mg), Ind (1.25 mg) as two capsules or both drugs as one tablet (S 5590), one single administration in a two way, randomly, cross-over design. Each administration was separated by a two week wash-out period. Plasma concentrations of Indapamide were determined by HPLC and plasma Perindopril and Perindoprilat (active metabolite of Per) concentrations by RIA , both up to 120 h post-last dose. Pharmacokinetic parameters of both drugs administered as tablet or capsules were compared by a three-ways analysis of variance (ANOVA) in Table 1.

Table 1 : Pharmacokinetic parameters in plasma (mean(s.d)).

		TABLET	CAPSULES	Conf. Interv. %
INDAPAMIDE	Cmax(ng/ml)	17 (3.6)	15 (3.7)	102-119
	AUC (ng.h/ml)	294 (79)	298 (79)	92-106
	tmax (h)	1.5	2	*
PERINDOPRIL				
	Cmax(ng/ml)	72 (20)	64 (24)	105-128
	AUC (ng.h/ml)	106 (32)	102 (43)	98-115
	tmax (h)	0.75	0.75	NS
PERINDOPRILAT				
	Cmax(ng/ml)	4.9 (2.7)	5.3 (2.6)	81-104
	AUC (ng.h/ml)	191 (76)	200 (66)	81-105
	tmax (h)	6	6	NS

* significant difference, NS no significant difference

Minor and well tolerated adverse events were observed in three out of eighteen subjects and no drop out was observed. Except for tmax the pharmacokinetic parameters of Indapamide did not differ between the two formulations. No significant differences were also observed for the pharmacokinetic parameters of Perindopril and Perindoprilat in plasma. In conclusion, the bioequivalence of the two formulations of Indapamide and Perindopril is established in terms of AUC and Cmax.

Key Words:
Hypertension, ACE Inhibitor, Diuretic.

C27

CARDIAC, RENAL AND VASCULAR EFFECTS OF A COMBINED TREATMENT WITH THE ACE INHIBITOR LISINOPRIL AND THE DIURETIC HYDROCHLOROTHIAZIDE IN SHR.

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The antihypertensive effects of ACE inhibitors are enhanced by concomitant administration of diuretics. In this study, we compared the effects of the ACE inhibitor lisinopril (L, 20 mg/kg/day) and hydrochlorothiazide (H, 12.5 mg/kg/day) with those of their combination (L+H) on the target organs of hypertension in salt - loaded (1 % NaCl) SHR. All treatments were given in drinking water, starting at the age of 11 weeks. After 6 months of treatment, systolic blood pressure (SBP) was determined in the conscious state. Rats were then placed in metabolic cages for 24 hours after which they were anesthetized and an arterial blood sample taken. The heart and the kidneys were isolated and weighed, and the thoracic aorta was taken out for determination of media collagen density (%). Table shows SBP (mm Hg), heart weight (g), diuresis (ml/h), natriuresis (mmol/24h), kaliuresis (mmol/24h) and creatinin clearance (creat; ml/h) (*: p<0.05 vs SHR; †: p<0.05 vs L+H)

	SBP	Heart weight	Diuresis	Natriuresis	Kaliuresis	Creat
SHR	220±9	1.68±.04	1.8±1	4.0±0.4	1.0±0.1	27.9±2.3
L	170±4*†	1.44±.06*†	1.9±.2	4.2±0.7	1.0±0.1	29.6±3.5
H	199±4*†	1.44±.03*†	2.2±.2	4.5±0.7	0.9±0.2	30.5±4.9
L+H	92±4*	1.13±.03*	1.8±1	5.6±0.6*	1.4±0.2*	45.5±6.2*

None of the treatments affected kidney weight (SHR: 1.43±0.03; L: 1.45±0.04; H: 1.44±0.06; L+H: 1.38±0.02g). Aortic collagen content decreased more with L+H than with L or H (SHR: 11.9± 0.5; L: 7.5±0.5*,†; H:9.5±0.5*,†; L+H: 5.5±0.3*).

Thus, in salt-loaded SHR, chronic treatment with L+H normalizes arterial pressure, exerts beneficial effects on cardiac mass and vascular structure that are more marked than those of lisinopril or hydrochlorothiazide alone and, in contrast with the individual treatments, has protective effects on renal function.

Key Words: SHR, ACE inhibition, diuretics, renal function

C28

CARDIAC AND VASCULAR EFFECTS OF A COMBINED TREATMENT WITH LOW DOSES OF AN ACE INHIBITOR AND INDAPAMIDE IN SHR.

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We have shown previously that combined treatment with low doses of indapamide (I; 0.24 mg/kg/day) and of the ACE inhibitor perindopril (P; 0.76 mg/kg/day) induced in SHR a decrease in blood pressure which was more marked than that induced by each individual treatment. This study was designed to assess the effect of a chronic oral treatment with I+P on cardiac and vascular morphology, as well as on endothelial function in SHR. After 3 months of treatment, systolic blood pressure (SBP) was measured in the conscious state. Rats were then placed in metabolic cages for 24 hours, after which they were anesthetized. The thoracic aorta was isolated and mounted in organ chambers, the abdominal aorta, carotid and femoral arteries were taken out after in vivo fixation, and histologic sections were stained with Sirius red. P+I markedly reduced SBP (from 223±4 to 131±4 and from 218±6 to 153±2 mm Hg 2h and 24h after treatment, respectively; both p<0.01) without affecting diuresis (SHR: 10±1; P+I 12±3 ml/24h), natriuresis (SHR: 1.11±.09; P+I: 1.17±0.09 mmoles/24h) or kaliuresis (SHR: 1.74±0.12; P+I: 1.69±0.14 mmoles/24h). Table shows results of morphometric analysis (*: p<0.05 vs SHR):

	Heart	Media area (x10³µm²)			Collagen (%)	
	weight (g)	Aorta	Carotid	Femoral	Heart	Aorta
SHR	1.56±.03	240±25	134±8	48±4	5.2±.3	14±2
P+I	1.25±.02*	187±17*	106±5*	38±2*	4.7±.2*	7±1*

In isolated aorta, hypertension was associated with the appearence of an endothelium - dependent contraction to acetylcholine (10^{-5}M; 1.53±0.27g) which was markedly reduced after I+P (0.14±0.05g; p<0.01 vs SHR). Thus, chronic treatment with low doses of perindopril and indapamide (administered at a non diuretic dose) induce a reduction in cardiac and vascular hypertrophy and fibrosis, and prevent the hypertension - induced alterations in endothelial function in SHR.

Key Words:
SHR, hypertrophy, endothelium, ACE inhibition