Acta Pharmacologica Sinica 1985 Jun; 6 (2) : 96-99

COMPARISONS OF EFFECTS OF HOE-498 AND ENALAPRIL IN ISOLATED GUINEA PIG HEARTS AND RAT MYOCARDIUM

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ABSTRACT In isolated guinea pig hearts Hoe-498 (1 mg/kg ig) attenuated the cardiac effects of angiotensin I (ANG I) but not angiotensin II (ANG II), and potentiated those of bradykinin (BK). Enalapril (MK-421) was without effect at this dose, but 30 mg/kg produced similar effects.

In rat myocardium. the converting enzyme (CE) activities after Hoe-498 (1 mg/kg ig) pretreatment (15 min, 1 & 6 h) were inhibited by 62, 70 and 19%, respectively. Enalapril (30 mg/kg ig) pretreatment yielded similar inhibitions (74, 76 and 50%, respectively).

The results indicate that Hoe-498 is c 30 times more potent as a CE inhibitor (CEI) than enalapril.

KEY WORDS Hoe-498; enalapril(MK-421);

Received 1984 Jun 6 Revised 1984 Aug 18

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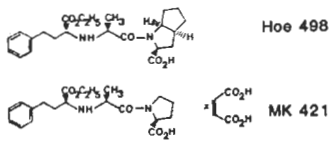

Fig 1. Structural formulae of Hoe-498 and enalapril (MK-421)

isolated heart; myocardium; kininase II inhibitors; bradykinin

The heart and/or coronary vasculature CE causes a conversion of ANG I to ANG II and induces a degradation of BK[1]. Hoe-498, a novel potent orally active CE inhibitor (CEI), attenuates the cardiac effects of ANG I and potentiates those of BK in isolated rat hearts[2,3]. Enalapril (MK-421) is another new potent CEI[4,5]. The chemical structures are shown in Fig 1. This study was designed to compare the actions of Hoe-498 and enalapril as CEI.

MATERIALS AND METHODS

Effects on ANG I, II and BK in isolated guinea pig hearts Guinea pigs (♀, 250±SD 18 g) were treated by gavage with Hoe-498 1 mg/kg, enalapril 30 mg/kg or vehicle (water) 2 ml/kg. After 1 h the hearts were isolated and perfused with Krebs-Henseleit solution[2]. Heart rate (HR), force of heart contraction (FC) and coronary flow (CF) were measured. The kinins were injected 10 or 100 ng/0.1 ml via aortic inflow.

CE activity in rat myocardium Wistar rats (♂, 280±11 g) were treated by gavage with Hoe-498 1 mg/kg or enalapril 30 mg/kg. Seven rats from each group were killed at 15 min, 1, 6 & 24 h, respectively by exsanguination under ether anesthesia. Tissue from the apex of left heart ventricle was homogenized, in a chilled polytrom tube, in water (1:5 w/v) containing 0.3% triton ×100 for 15 s followed by sonification for 5 s. After centrifugation at 27138 ×g at 4℃ for 15 min, CE was assayed in the supernatant fluorometrically[6] using carbobenzoxy-phenylalanyl-histidyl-leucine (Z-Phe-His-Leu) as substrate. Fluorescence (λ_{ex}360 nm, λ_{em}500 nm) was measured within 1 h.

RESULTS

Effects on ANG I, ANG II and BK (Tab 1) In control hearts ANG I (100 ng) and ANG II (10 ng) decreased CF and FC without altering HR. Conversely, BK (10 ng) increased CF and FC, but HR remained unchanged.

The effects of ANG I on CF and FC were inhibited by Hoe-498 1 mg/kg, a dose which potentiated the effect of BK. Enalapril 1 mg/kg did not attenuate the ANG I effects, but potentiated the action of BK on CF. Enalapril 30 mg/kg blocked the ANG I action on CF and FC and potentiated the BK-mediated increase in CF and FC.

ANG II effects were unchanged in Hoe-498 or enalapril treated guinea pigs.

CE activity in rat myocardium (Tab 2) The activities of CE in myocardium of rats after gavage with Hoe-498 (1 mg/kg) were inhibited by 62, 70, 19 and 22%, respectively at 15 min, 1, 6 and 24 h. The corresponding values for enalapril (30 mg/kg) were −74, −76, −50 and +70%.

DISCUSSION

The present results demonstrate that the two CEI, Hoe-498 and enalapril (MK-421), inhibit the effects of ANG I but not ANG II, and potentiate those of BK on CF and FC. These findings are consistent with our previous observations[2,3]. Although the effects of ANG and BK on FC in isolated guinea pig heart differ greatly from the results in isolated rat heart, it is in line with earlier report[7]. The discrepancy is probably due to differences not only in animal species but also in doses of peptide used. A reduction of FC induced by ANG, probably best explained by the reduced blood flow. BK effects were opposite to those of ANG with marked vasodilation, increased CF and enhanced FC.

Direct evidence for cardiac CE inhibition

Tab 1. Changes of coronary flow and force of heart contraction induced by ANG I, ANG II and bradykinin (BK) in isolated hearts of guinea pigs (12/group) pretreated with Hoe-498 or enalapril. $\bar{x}\pm SD$. Compared to control *p>0.05, **p<0.05, ***p<0.01

	Coronary flow (ml/g/min)						Force of heart contraction (g)					
	ANG I (100 ng)		ANG II (10 ng)		BK (10 ng)		ANG I (100 ng)		ANG II (10ng)		BK (10 ng)	
	$-\bar{\Delta}$	%	$-\bar{\Delta}$	%	$+\bar{\Delta}$	%	$-\bar{\Delta}$	%	$-\bar{\Delta}$	%	$+\bar{\Delta}$	%
Control	3.03±0.76	100	1.52±0.59	100	3.41±0.55	100	0.58±0.14	100	0.55±0.17	100	0.56±0.10	100
Hoe-498 1 mg/kg	1.41±0.21 ***	47	1.47±0.38	86	7.53±0.80 ***	221	0.45±0.07 ***	78	0.65±0.24	118	0.74±0.14 ***	132
Enalapril 1 mg/kg	2.59±0.38 *	85	---	--	5.00±2.04 **	147	0.51±0.10	88	---	--	0.66±0.14 *	118
Enalapril 30 mg/kg	1.66±0.45 ***	55	1.42±0.42	93	6.15±0.90 ***	180	0.44±0.07 ***	81	0.60±0.24	109	0.68±0.10 ***	121

Tab 2. Inhibition of converting enzyme activity (pmol His-Leu/mg protein/min) in myocardium of rats after a single gavage of Hoe-498 or enalapril. 28 rats/drug. $\bar{x}\pm SD$. Compared with control *p>0.05, ** p<0.05, ***p<0.01

	mg/kg	15 min	1 h	6 h	24 h
Hoe-498	0	112±26	131±55	60±12	51±12
	1	42±33***	40±16***	48±11**	39±8**
	Change	−62%	−70%	−19%	−22%
Enalapril	0	165±49	167±85	157±60	122±47
	30	43±20***	41±12***	79±30***	207±77**
	Change	−74%	−76%	−50%	+70%

is provided in this study by the demonstration that CE-activity is markedly reduced following treatment with Hoe-498 and enalapril, the effects persisting up to 24 h after one single oral dose. The late increase of CE-activity in enalapril treated group is perhaps due to enzyme induction.

The 2 non sulfhydryl CEI produced similar effects in these 2 different experiments. From the results it is evident that Hoe-498 is 30 times more potent than enalapril, but exhibited the same pharmacological profile. Hoe-498 produced a somewhat longer action on the heart at equi-effective doses. These effective action of local CE inhibition in the heart is of important value to clinical therapeutics, since orally active CEI such as enalapril and captopril have been introduced into the treatment of hypertension and congestive heart failure[8],

ACKNOWLEDGMENTS We are grateful to Prof Dr G S Ding and Dr M A Petty for their excellent editorial assistance.

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Hoe-498 和 enalapril 在离体豚鼠心脏和大鼠心肌作用的比较

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提要　预先灌服过 Hoe-498 1 mg/kg 的离体豚鼠心脏，减弱血管紧张素Ⅰ的心脏作用；可加强缓激肽的作用。Enalapril 1 mg/kg 对血管紧张素Ⅰ和舒缓激肽无作用，30 mg/kg 才产生相似的作用。两药对血管紧张素Ⅱ的作用都无变化。

预先灌服 Hoe-498 1 mg/kg 后 15 min，1 和 6 h 测定大鼠心肌转换酶活力，分别抑制 62,70 和 19%。Enalapril 30 mg/kg 分别抑制 74,76 和 50%。结果指出 Hoe-498 较 enalapril 强 30 倍。

关键词　Hoe-498；enalapril (MK-421)；离体心脏；心肌；激肽酶Ⅱ抑制剂；舒缓激肽

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