

Hypotension after Administration of the First Dose of Angiotensin-Converting Enzyme (ACE) Inhibitors in Patients with Congestive Heart Failure

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ABSTRACT

First-dose hypotension refers to an observed reduction in blood pressure after the administration of the first dose of ACE inhibitors in patients with congestive heart failure. We aimed to compare the first-dose responses of low-dose enalapril and accupro in patients with stable symptomatic chronic heart failure. Methods: Single blind, randomized study. Patients (N=80) with chronic heart failure due to ischemic heart disease, NYHA II-IV, ejection fraction<40%, age>18 year were randomized to receive a single dose of 2,5 mg enalapril or 5 mg accupro. Ambulatory blood pressure monitoring started 2h before the study medication was given, and continued for at least 10h after the medication. Results: The maximum drop in blood pressure appeared approximately 4h after dose administration in both groups, and was more pronounced in the enalapril group. Patients in the enalapril group had a significantly higher incidence of asymptomatic hypotension. No symptomatic hypotension requiring a change in medication or a prolongation of hospitalization was observed. Conclusion: A low dose of accupro is well tolerated at initiation of ACE inhibitor therapy in patients with chronic heart failure and causes less first-dose hypotension than a low dose of enalapril.

KEYWORDS: first-dose hypotension, congestive heart failure, enalapril, accupro

First-dose hypotension has been recognized as a potential limiting factor in the use of ACE inhibitors in the treatment of chronic heart failure. Concerns regarding first-dose hypotension may increase the risk of renal, myocardial or cerebral hypoperfusion [1,2,3]. The incidence of first-dose hypotension after ACE inhibitors reported in large clinical trials is small, varying from 0,7% to 9,4% [4,5,6]. Some smaller trials have reported a much higher incidence of first-dose hypotension, affecting as many as one-third of the patients [7]. The origin at this response remains unclear and is probably not the same as the reduction in blood pressure seen after chronic use. It may partly reflect the activation at the circulation and tissue-based rennin-angiotensin system. The hypotension effect of ACE inhibitors is initially proportional to the inhibition of the enzyme; on the other hand no correlation of pre-treatment plasma rennin activity with the hypotensive effect of ACE inhibition has been demonstrated during long-term administration [8]. However, this may be an expression of the range of individual sensitivity or responsiveness to the drug and to the dose used. Some authors stress the importance of the vasovagal reaction to the first dose [9]. From noted, we aimed to compare the first-dose responses of low-dose enalapril and accupro in patients with stable symptomatic chronic heart failure.

MATERIAL AND METHOD

Randomized, single blind study was conducted in 80 patients with stable heart failure due to ischemic heart disease, with a left ventricular ejection fraction less than 40%. The diagnosis was confirmed by clinical history and by physical, echocardiographic and electrocardiographic examinations before treatment. All patients had stable renal function, with serum creatinine less than 200 $\mu\text{mol/l}$ and potassium less than 5 mmol/l. Further exclusion criteria were: serum sodium less than 100 mgHg, unstable angina pectoris. The patients were randomized to receive either 2,5 mg enalapril or 5mg accupro. The study protocol was approved by the local research and ethics

review committee. All patients gave their written informed consent to take part in the study. The baseline characteristics of both groups are shown in Tab.1.

	Enalapril	Accupro	Value
Patients	n=41	n=39	ns
Male	38 (92,7%)	35 (90%)	ns
Female	3 (7,3%)	4 (10%)	ns
Age (years)	64,3 \pm 9,4	65,4 \pm 9,3	ns
Weight (kg)	78,8 \pm 14,0	79,9 \pm 14,2	ns
BMI (kg/m²)	27,4 \pm 4,0	27,6 \pm 3,9	ns
NYHA class			
II	17 (41%)	17 (43,4%)	ns
III	21 (51,2%)	20 (52,5%)	ns
IV	3 (7,8%)	2 (4,1%)	ns
Etiology of CHF			
IHD-post MI	41	39	ns
Ejection fraction	34,2 \pm 6,5	34,6 \pm 6,1	ns
Creatinine (mol/l)	104,4 \pm 27,2	102,9 \pm 23,4	ns
Potassium (mmol/l)	4,2 \pm 0,4	4,3 \pm 0,4	ns

BMI – Body mass index
IHD – ischemic heart disease
MI – myocardial infarct

Tab.1 Baseline clinical and biochemical parameters.

Diuretics were withdrawn for 24h before treatment. Other concomitant medication was unchanged. The first morning (at 07.30) a blood sample was taken. Blood pressure was measured every 15 min. for 2h. The first three measurements were excluded and the baseline blood pressure was calculated from the mean of the fourth to eight measurements. Assessment was to begin at the same time of the day for all patients. After the first eight measurements 2,5 mg enalapril and 5 mg accupro were given. Blood pressure was then measured every 15 min. for the next 10h. It was recommended to continue the measurements for the next 12h at 30 min. intervals. The patients were on bed rest for at least the first 12h of the study. The baseline laboratory parameters were measured using standard methods. The systolic blood pressure, the diastolic blood pressure and the mean value of arterial pressure were used for statistical analysis. Repeated-measures analysis of variance was applied followed by multiple Bonferroni comparisons, with treatment effects compared at each time point. Effects with a p value <0,05 were regarded as significant. Data are shown as mean ±S.D.

RESULTS AND DISCUSSION

The baseline blood pressure (BP) values rates are shown in Tab.2. There was no significant difference between the two groups.

	Enalapril (n=41)	Accupro (n=39)	
Systolic BP	129,4±19,8	129±19,1	ns
Diastolic BP	72,9±11,8	73,2±11,1	ns
MAP	91,7±13,1	91,8±12,4	ns

BP = blood pressure
MAP – mean arterial pressure

Tab.2 Vaseline blood pressure values.

The minimal systolic blood pressure values appeared 4h after the morning dose of enalapril and 4,5h after the morning dose of accupro. The diastolic blood pressure and the mean arterial pressure appeared 4,5h after the morning dose in both groups. All values were statistically highly significantly different from baseline values (all p<0,001). The minimal blood pressure values during the study period and the statistical significance of the differences between the groups is shown in Tab.3.

	Enalapril (n=41)	Accupro (n=39)	p
Systolic BP	100,8±17,4	112±16,2	<0,001
Diastolic BP	53,0±10,1	60,7±9,7	<0,001
MAP	70,3±12,3	79,3±10,6	<0,001

Tab.3 Minimal blood pressure values

A decrease in mean arterial pressure of more than 20 mmHg appeared in 21 (51%) of the patients in the enalapril group and in 5 (13%) patients in the accupro group (p<0,001). A blood pressure fall of more than 20 mmHg and an absolute value of less than 90/60 mmHg appeared in one patient in the accupro group and in 8 patients in the enalapril group (p<0,001). Systolic blood pressure below 90 mm Hg and diastolic blood pressure below 60 mm Hg in at least on measurement appeared in 10 (24%) of the patients in the enalapril group and in 1 (2,5%) patient in the accupro group (p<0,001) (Tab.4 and Tab.5). There were 30 (75%) asymptomatic episodes of hypotension in the enalapril group, and only three (8%) in the accupro group. There was one episode of symptomatic hypotension requiring pharmacological treatment, or prolongation of hospitalization.

	Enalapril (n=41)	Accupro (n=39)	p
SBP=90 mmHg	11 (27%)	2 (5%)	<0,001
SBP=90mmHg and DBP=60mmHg	10 (24%)	1 (2,5%)	<0,001
DBP=60mmHg	31 (75%)	18 (45%)	<0,001

SBP = systolic blood pressure
DBP – diastolic blood pressure

Tab.4 Number of patients with SBP=90mmHg and/or DBP=60mmHg.

	Enalapril (n=41)	Accupro (n=39)	p
SBP=90 mmHg	33 (80%)	4 (10%)	<0,001
SBP=90mmHg and DBP=60mmHg	30 (75%)	3 (8%)	<0,001
DBP=60mmHg	20 (50%)	7 (18%)	<0,001

Tab.5 Number of episodes with SBP=90mmHg and/or DBP=60mmHg.

The high-risk population of patients was defined in the study protocol at rest symptoms of heart failure (NYHA IV-) and/or serum creatinine concentration greater than 150 µmol/L and/or age over 70 years. Asymptomatic hypotension appeared in the high-risk population in 12 patients (enalapril group) and in 2 patients in the accupro group (p<0,001).

First-dose hypotension is defined as a mean arterial blood pressure decrease of more than 20 mmHg and/or of peak value less than 90 mmHg of systolic and/or 60 mm Hg of diastolic BP. Both these criteria were fulfilled in 8patients in the enalapril group, but only one in the accupro group (p<0,001). In terms of the number of patients, the number of episodes was at least 10 times higher in the enalapril group than in the accupro group,

which mean an 10 times higher incidence of episode per patient ($p < 0,001$) in the enalapril group.

Although first-dose hypotension is generally considered to be a class effect of ACE inhibitors, preliminary reports documented already differences in first-dose hypotension induced by ACE inhibition in patients with chronic heart failure [4]. The study of Mclay et al [9] showed that in the group as a whole, the magnitude of the fall in BP after the first dose correlated significantly with starting plasma levels of angiotensin II, atrial natriuretic peptide, aldosterone, and rennin. The use of high fixed dose of an ACE inhibitor may produce prolonged hypotensive affects resulting in end-organ acute ischemia [10].

The first-dose hypotension is frequent in patients with chronic heart failure, where the tissue rennin-angiotensin system is stimulated and in a failing heart nearly 80% of

ACE activity is shifted to the tissue [11]. McFadyen et al [4] found similar plasma ACE inhibition with both enalapril and accupro associated with different responses in BP, suggesting differences in penetration and interaction with the tissue rennin-angiotensin systems and therefore a specific action of each drug. Accupro is a lipophilic agent with high oral bioavailability [22]. At is therefore, likely to achieve sufficiently high tissue concentrations to complete with its active diacide metabolic quinaprilat for binding with ACE. One of the reasons for under prescribing of ACE inhibitors in treatment of heart failure could be fear of first hypotension. Our study demonstrated differences in BP response to the first-dose during initiation of treatment of congestive heart failure with various ACE inhibitors. These observations are of practical importance, especially for doctors initiating treatment for congestive heart failure with ACE inhibitors in their daily practice.

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Гипотензия после приема первой дозы ингибитора ангиотензин-превращающего фермента у больных застойной сердечной недостаточностью

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Р Е З Ю М Е

Целью исследования являлась оценка гипотензии после приема первой дозы ингибиторов ангиотензин-превращающего фермента (ИАПФ) эналаприла и аккупро у больных застойной сердечной недостаточностью. Материал и методы: 80 пациентов с застойной сердечной недостаточностью на фоне ишемической болезни сердца (NYHA II-IV функциональный класс, старше 18 лет) были рандомизированы в зависимости от приема первой дозы ИАПФ эналаприла (2,5 mg) или аккупро (5 mg). До начала исследования проведены клинические и основные лабораторные исследования. Измерение артериального давления проводили за 2 часа до приема ИАПФ и продолжали в течение 10 часов после приема препаратов. Результаты: максимальное снижение артериального давления наблюдалось через 4 часа после приема первой дозы эналаприла и 4,5 часа спустя приема первой дозы аккупро. Выявлено достоверно больше случаев бессимптомной гипотензии в группе больных, леченных эналаприлом. Ни одного случая симптомной гипотензии, который потребовал бы отмены препарата не отмечено. Выводы: Начало лечения больных застойной сердечной недостаточностью на фоне ишемической болезни сердца низкими дозами аккупро сравнительно реже вызывает развитие гипотензии после приема первой дозы, чем при приеме низких доз эналаприла.

Ключевые слова: гипотензия, застойная сердечная недостаточность, эналаприл, аккупро