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First-dose hypotension after angiotensin-converting enzyme (ACE) inhibitors in chronic heart failure: a comparison of enalapril and perindopril

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Abstract

Background: 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. *Aim:* To compare the first-dose responses of low-dose enalapril and perindopril in patients with stable symptomatic chronic heart failure. *Methods:* Single blind, randomised, multicenter, parallel, prospective study. Patients ($N = 298$) with chronic heart failure due to ischemic heart disease or dilated cardiomyopathy, NYHA II–IV, ejection fraction $< 40\%$, age > 18 years, naive to ACE inhibitors or ATI-receptor blocker, were randomised to receive a single dose of 2.5 mg enalapril or 2.0 mg perindopril. Baseline laboratory and clinical examinations were performed before entry into the study. Ambulatory blood pressure monitoring started 2 h before the study medication was given, and continued for at least 10 h after the medication. *Results:* The maximum drop in blood pressure appeared approximately 4 h 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 hospitalisation was observed. *Conclusion:* A low dose of perindopril 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. © 2000 Published by European Society of Cardiology.

Keywords: Hypotension; Congestive heart failure; Enalapril; Perindopril

1. Introduction

Several angiotensin-converting enzyme inhibitors (ACEI) have shown to be valuable in the management of chronic heart failure [1,2]. Their efficacy has been well-documented for mild, moderate, and severe chronic heart failure. ACE inhibitors have been shown to relieve symptoms, improve haemodynamic function, and reduce mortality and morbidity, regardless of the aetiology of the syndrome. They form the cornerstone of treatment of chronic heart failure [3]. A series of case reports and small studies showed a considerable fall in blood pressure in response to the first dose of an ACE inhibitor in patients with chronic heart failure [4–6]. The origin of 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 of the circulation and

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tissue-based renin–angiotensin system. The hypotensive effect of ACE inhibitors is initially proportional to the inhibition of the enzyme; on the other hand, no correlation of pre-treatment plasma renin activity with the hypotensive effect of ACE inhibition has been demonstrated during long-term administration [7]. 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 [8].

We conducted a randomised, multicenter, single-blind, parallel-group study in patients with stable heart failure, naive to ACE inhibitors and angiotensin receptor blockers. The patients were admitted to hospital for initiation of treatment with ACE inhibitors.

2. Patients and methods

A single-dose, multicenter, randomised, single-blind parallel-group study was conducted in 298 patients with stable heart failure. Ten hospitals in the Czech and the Slovak Republics were involved. We selected patients with chronic heart failure due to ischemic heart disease or to dilated cardiomyopathy, with a left ventricular ejection fraction less than 40%, who were symptomatic on diuretic treatment. None had a significant fluid imbalance by clinical criteria, or an acute decompensation during the preceding 3 months. 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 μmol/l and potassium less than 5 mmol/l. Further exclusion criteria were: serum sodium less than 135 mmol/l, systolic blood pressure less than 100 mmHg, unstable angina pectoris, etc. The patients were randomised to receive either 2.5 mg enalapril or 2.0 mg perindopril. 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 Table 1.

Table 1
Baseline clinical and biochemical parameters

	Enalapril	Perindopril	*P* value
Patients	$n = 151$	$n = 147$	
Male	88 (58.3%)	93 (63.3%)	ns
Female	63 (41.7%)	54 (36.7%)	ns
Age (years)	64.3 ± 9.4	65.4 ± 9.3	ns
Weight (kg)	78.8 ± 14.0	79.9 ± 14.2	ns
BMI (kg/m^2)	27.4 ± 4.0	27.6 ± 3.9	ns
NYHA class			
II	60 (39.7%)	65 (44.2%)	ns
III	76 (50.3%)	74 (50.3%)	ns
IV	15 (9.8%)	8 (5.5%)	ns
Etiology of CHF			
IHD-post MI	82 (54.3%)	78 (53.1%)	ns
Other	69 (45.7%)	69 (46.9%)	ns
Ejection fraction(%)	34.2 ± 6.5	35.1 ± 6.1	ns
Creatinine (mol/l)	104.4 ± 24.2	102.9 ± 23.4	ns
Potassium(mmol/l)	4.2 ± 0.4	4.3 ± 0.4	ns

3. Procedure

Diuretics were withdrawn for 24 h before treatment. Other concomitant medication was unchanged. The first morning (at approx. 07.30 h) a blood sample was taken. Blood pressure was measured (Meditech-ABPM 03) every 15 min for 2 h. The first three measurements were excluded and the baseline blood pressure was calculated from the mean of the fourth to eighth measurements. The morning concomitant medication was given with a light breakfast after blood sampling and before the first measurement. Assessment was to begin at the same time of the day for all patients. After the first eight measurements the code was broken and 2.0 mg perindopril or 2.5 mg enalapril were given. Blood pressure was then measured every 15 min for the next 10 h. The values were recorded to protocol every 30 min. It was recommended, but not obligatory, to continue the measurements for the next 12 h at 30-min intervals. The patients were on bed rest for at least the first 12 h of the study.

4. Laboratory and statistical analysis

The baseline laboratory parameters were measured in local laboratories, using standard methods. The systolic blood pressure, the diastolic blood pressure and the mean value of triplicate mean arterial pressure recordings were used for statistical analysis, all as absolute values and as changes from baseline at each time point. Repeated-measures analysis of variance was applied followed by multiple Bonferroni comparisons, with treatment effects compared at each time point. The episodes of asymptomatic hypotension were compared using the Mann–Whitney test. Effects with a P value < 0.05 were regarded as significant. Data are shown as mean ± S.D.

5. Results

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

Table 2
Baseline blood pressure values[a]

	Enalapril ($n = 151$)	Perindopril ($n = 147$)	P value
Systolic BP	129.4 ± 19.8	129.1 ± 19.1	ns
Diastolic BP	72.9 ± 11.8	73.2 ± 11.1	ns
MAP	91.7 ± 13.1	91.8 ± 12.4	ns

[a]*Abbreviations:* BP, blood pressure; MAP, mean arterial pressure.

Table 3
Minimal blood pressure values

	Enalapril ($n = 151$)	Perindopril ($n = 147$)	P
Systolic BP	100.8 ± 17.4	112.6 ± 16.2	< 0.001
Diastolic BP	53.0 ± 10.1	60.7 ± 9.7	< 0.001
MAP	70.3 ± 12.5	79.3 ± 10.6	< 0.001

The minimal systolic blood pressure values appeared 4 h after the morning dose of enalapril and 4.5 h after the morning dose of perindopril. The minimal diastolic blood pressure and the mean arterial pressure appeared 4.5 h 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 difference between the groups is shown in Table 3.

The changes in blood pressure from the baseline during the first 10 h after the drug administration for both groups are shown in Figs. 1–3. Measurement of heart rate was not part of the official protocol, and was carried out only in one centre, in 32 patients. In this group the heart rate did not significantly change from baseline during 10 h (Fig. 4). A decrease in mean arterial pressure of more than 20 mmHg appeared in 76 (50.3%) of the patients in the enalapril group and in 22 (14.9%) patients in the perindopril 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 perindopril group and in 31 patients in the enalapril group ($P < 0.001$). Systolic blood pressure below 90 mmHg and diastolic blood pressure below 60 mmHg in at least

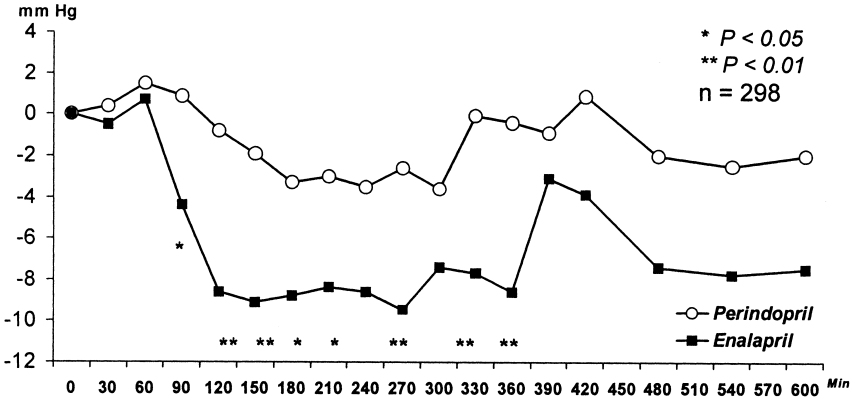

Fig. 1. Changes of systolic blood pressure from baseline.

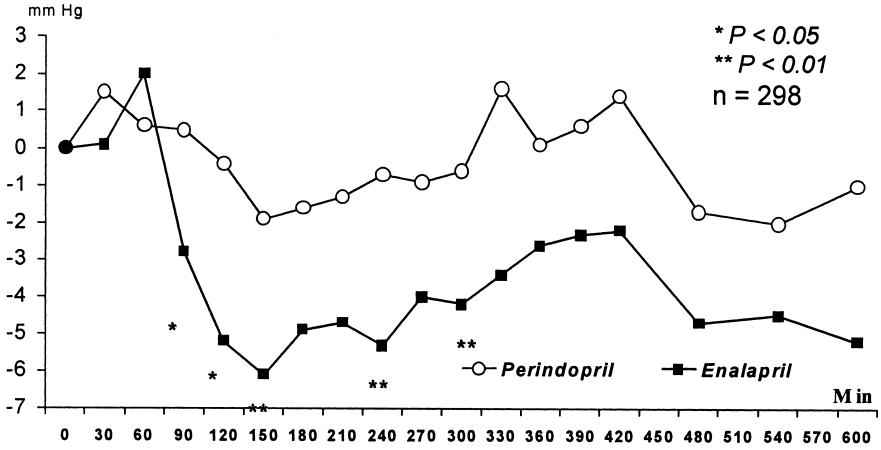

Fig. 2. Changes of diastolic blood pressure from baseline.

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

	Enalapril ($n = 151$)	Perindopril ($n = 147$)	P
SBP = 90 mmHg	45 (29.5%)	5 (3.4%)	< 0.001
SBP = 90 mmHg and DBP = 60 mmHg	44 (29.1%)	4 (2.7%)	< 0.001
DBP = 60 mmHg	116 (76.8%)	69 (46.9%)	< 0.001

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

	Enalapril	Perindopril	P
SBP = 90 mmHg	113	7	< 0.001
SBP = 90 mmHg and DBP = 60 mmHg	102	6	< 0.001
DBP = 60 mmHg	597	332	< 0.001

one measurement appeared in 44 (29.1%) of the patients in the enalapril group and in four (2.7%) patients in the perindopril group ($P < 0.001$) (Tables 4 and 5). There were 102 asymptomatic episodes of hypotension in the enalapril group, and only six in the perindopril group. There was one episode of symptomatic hypotension in the enalapril group and none in the perindopril group. There were no episodes of hypotension requiring pharmacological treatment, or prolongation of hospitalisation.

The at-risk population of patients was defined in the study protocol as rest symptoms of heart failure (NYHA IV-24 patients) and/or serum creatinine concentration greater than 150 μmol/l (13 patients) and/or age over 70 years (122 patients). Asymptomatic hypotension appeared in the at-risk population in 58 patients in the enalapril group and in four patients in the perindopril group ($P < 0.001$).

6. Discussion

First-dose hypotension has been recognised 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 [9].

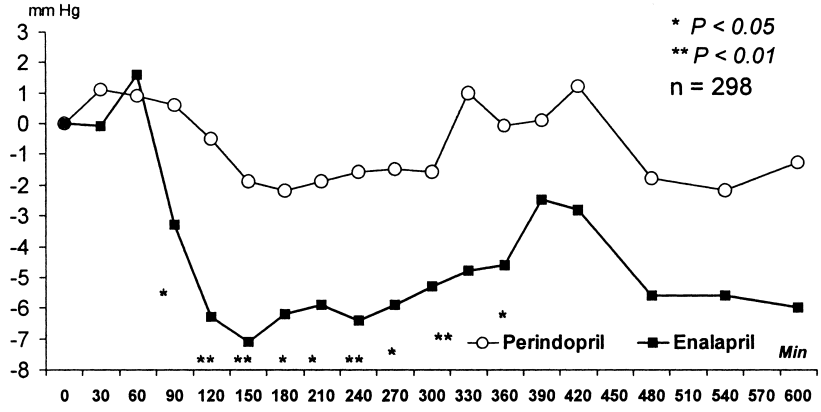

Fig. 3. Changes of mean blood pressure from baseline.

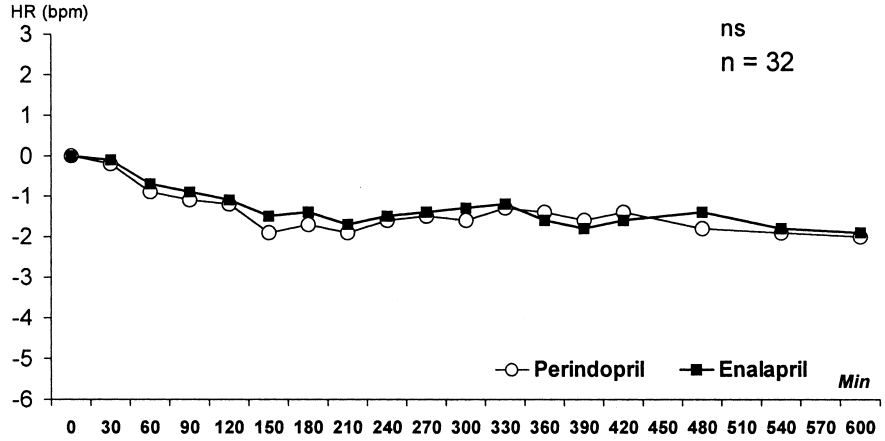

Fig. 4. Changes in heart rate from baseline.

The incidence of first-dose hypotension after ACE inhibitors reported in large clinical trials is small, varying from 0.7% in the SAVE trial [10] to 9.4% in the CCS-1 trial [11]. This variation reflects differences in study design, in patient selection, in the definition of first-dose hypotension, and in drug selection. The major reason for the low number of these events reported is a very infrequent use of ambulatory blood pressure monitoring and thus, the incidence of less than 10% reflects only symptomatic or casually measured hypotension [12]. Some smaller trials have reported a much higher incidence of first-dose hypotension, affecting as many as one-third of the patients [13].

There is no formal definition of first-dose hypotension, the extent and duration of which can vary widely between patients. Reid et al. [5] recommends a drop in systolic blood pressure of more than 20 mmHg, and diastolic blood pressure of more than 10 mmHg as the definition of first-dose hypotension. This definition has the main disadvantage of not affecting absolute baseline and the peak values. If the baseline blood pressure was high ($>140/90$), then this decrease would probably be positive, and if the baseline value were nearer to hypotensive values (90–100/60–65 mmHg), then a much smaller blood pressure decrease could be of critical value. Therefore, we have used a modified version of this definition. 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 mmHg of diastolic BP. Both these criteria were fulfilled in 31 patients in the enalapril group, but only two in the perindopril group ($P < 0.002$). In terms of the number of patients, the number of episodes was at least 16 times higher in the enalapril group than in the perindopril group, which means an 18 times higher incidence of episode per patient (0.75 vs. 0.04, $P < 0.001$) 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. Variation in their propensity to induce this effect may reflect important and clinically relevant agent-specific differences [4]. The main interest of our study is to confirm some amplitude of difference than previously reported between enalapril and perindopril in the maximal fall in the mean blood pressure, but in a much larger population.

The precise etiology of ACE inhibitor first-dose remains unclear, with several mechanisms proposed, including activation of the Bezhold–Jarisch reflex by vagally mediated hypotension and bradycardia [14]. However, none of the 32 patients involved in heart rate measurement in our study had first-dose-induced bradycardia, so we believe that this reflex has little relevance to the first-dose blood pressure response, even if it can explain some rare cases. High plasma renin and angiotensin levels prior to administration of an ACE inhibitor induce a great probability for an acute fall in BP and thus, pre-treatment levels of circulatory angiotensin-II may also be considered a risk factor for first-dose hypotension [15]. The study of McLay et al. [16] 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 renin, but individual data showed, however, that the two patients with the greatest fall in BP did not have the most activated renin–angiotensin–aldosterone system. ACE inhibitors modify the kallikrein–kinin system and ACE is identical to kininase II, and its inhibition by ACEI prevents the breakdown of the endogenous vasodilator bradykinin. However, this action again seems to be a class effect, without any difference being demonstrated between ACE inhibitors [17].

ACE inhibitor dosage and duration of action are also to be considered for the risk of first-dose hypotension. The use of a high fixed dose of an ACE inhibitor may produce prolonged hypotensive effects resulting in end-organ acute ischemia [18] and thus, the use of a much lower initial dose to reduce the duration of ensuing hypotension has been recommended [19]. However, there are conflicting reports about the association between the initial dose of ACE inhibitor and the magnitude of the first-dose hypotensive effect [16,20].

Finally, ACE binding kinetics may play a role [12]. This could also explain why first-dose hypotension is so frequent in patients with chronic heart failure, where the tissue renin–angiotensin system is stimulated, and in a failing heart nearly 80% of ACE activity is shifted to the tissue [21]. MacFadyen et al. [4] found similar plasma ACE inhibition with both enalapril and perindopril associated with different responses in BP, suggesting differences in penetration and interaction with the tissue renin–angiotensin systems and, therefore, a specific action of each drug. Perindopril is a lipophilic agent with high oral bioavailability [22], it is, therefore, likely to achieve sufficiently high tissue concentrations to compete with its active diacide metabolite perindoprilat for binding with ACE. This competition may underlie the progressive onset of action noted with perindopril administration, and explain the lack of significant first-dose hypotension effect with this agent.

7. Conclusion

One of the reasons for underprescribing of ACE inhibitors in treatment of heart failure could be fear of first-dose hypotension. Our study demonstrated differences in BP response to the first-dose during initiation of treatment of congestive heart failure with various ACE inhibitors. Although we observed only one symptomatic episode in the enalapril group, the incidence of asymptomatic first-dose hypotension was significantly lower in the perindopril group compared with the group of enalapril, not only in the general population, but also in high-risk patients. Knowledge of the differential effects of various ACE inhibitors on first-dose hypotension is useful in choosing the appropriate ACE inhibitor at initiation of therapy in high-risk patients who are likely to develop hypotension. 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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