

PLASMA ENDOTHELIN IN CONGESTIVE HEART FAILURE: EFFECT OF THE ACE INHIBITOR, FOSINOPRIL

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REZUMAT

Endotelina plasmatică în insuficiența cardiacă congestivă - efectul unui inhibitor al enzimei de conversie - Fosinopril

Obiective: Studiul evaluează influența tratamentului cu un inhibitor al enzimei de conversie, fosinopril, asupra nivelurilor plasmatică de endotelină la pacienții cu insuficiență cardiacă congestivă și relația între endotelina plasmatică și unii parametrii ca exerciciu cu bicicleta, echocardiografia, scorul insuficienței cardiace și presiunea arterială.

Metode: Endotelina plasmatică a fost măsurată la 34 pacienți cu I.C. moderată/severă în studiul randomizat, placebo-controlat "Studiul Eficacității și Siguranței Fosinoprilului".

Rezultate: Pacienții au avut niveluri ridicate de endotelină plasmatică înainte de tratament ($3,5 \pm 1,2$ pg/ml) comparativ cu voluntarii sănătoși ($2,0 \pm 0,4$ pg/ml).

Tratamentul cu fosinopril timp de 12 săptămâni a scăzut endotelina plasmatică în contrast cu o creștere nesemnificativă în grupul placebo.

Concluzii: Tratamentul pacienților cu I.C. congestivă cu acest inhibitor al enzimei de conversie (fosinopril) reduce nivelul endotelinei plasmatică la niveluri normale. Relația între endotelina plasmatică și parametrii clinici indică faptul că endotelina poate juca un rol patologic în progresia I.C. congestive.

Cuvinte cheie: insuficiență cardiacă, endotelină, endotelium, inhibitori ai enzimei de conversie.

ABSTRACT

Objectives: The study evaluates the influence of treatment with the angiotensin-converting enzyme inhibitor, fosinopril, on the plasma endothelin level in patients with congestive heart failure and the relationship between plasma endothelin and clinical study parameters (bicycle exercise test, echocardiography, heart failure score and blood pressure).

Methods: Plasma endothelin was measured in 34 patients with moderately/severe congestive heart failure at randomisation in the fosinopril/placebo-controlled study "Fosinopril Efficacy and Safety Trial" and at the end of the 12-week study period.

Results: The patients had elevated pre-treatment plasma endothelin concentrations ($3,5 \pm 1,2$ pg/ml, mean \pm s.d., $n = 34$) compared with healthy volunteers ($2,0 \pm 0,4$ pg/ml, $n = 21$, $P < 0,0001$).

Treatment with fosinopril for 12 weeks lowered plasma endothelin from $3,5 \pm 1,2$ to $0,7$ pg/ml ($n = 18$, $P < 0,005$), in contrast to the non-significant increase in the placebo-treated group ($3,5 \pm 1,3$ to $4,3 \pm 2,5$ pg/ml, $n = 16$). A multiple regression analysis for baseline study parameters demonstrated a significant relationship between plasma endothelin and exercise test duration and a composite heart failure score classification ($r = 0,53$, $P < 0,001$).

Conclusions: Treatment of patients with congestive heart failure with the angiotensin-converting enzyme inhibitor, fosinopril, reduce the elevated plasma endothelin level to normal values. The relation between plasma endothelin and clinical parameters indicates that endothelin may play a pathophysiological role in the progression of congestive heart failure.

Key words: RAAS, heart failure, endothelin, endothelium, ACE-inhibitors.

Introduction

Endothelin (ET) is a potent endothelium-derived vasoactive peptide with long-lasting vasoconstrictor (1) and growth-promoting properties (2). Recent studies on patients with congestive heart failure (CHF) demonstrated elevated plasma ET (3, 4) that correlated positively with the rise in pulmonary pressure (5) and the New York Heart Association classification (3, 6).

Treatment with an angiotensin-converting enzyme (ACE) inhibitor reduces peripheral vascular resistance, reverses structural vascular alterations (7), has sympatholytic effects (8), enhances exercise performance and reduces mortality

in CHF (9, 11). It is unclear from the results of experimental studies whether (12, 13) or not (14, 15) angiotensin II stimulates ET release. However, ACE inhibition reduced the stimulating effect of serum on ET secretion from cultured human endothelial cells (14).

Fosinopril is an ACE inhibitor containing a phosphorus atom instead of a sulfhydryl, that plays an important role in binding to the angiotensin-converting enzyme. It has a high lipid solubility which results in dual excretion, through the biliary tract as well as the usual renal route (16).

This study was designed to determine the effect of treatment with the ACE inhibitor, fosinopril, on elevated plasma ET in patients with congestive heart failure and the

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relation between plasma ET and clinical parameters characterizing the condition of the patients.

2. Methods

2.1. Patient population

Forty-four patients (33 men and 11 women) with stable moderately severe (New York Heart Association II or III) CHF with a mean age of 66 years (range 47 - 75) were primarily enrolled. However, during the 12-week study period, 10 patients were withdrawn (6 men and 4 women, 63 years (range 48 - 75)) due to worsening heart failure (5), endocarditis (1) or sampling failure (4). In total, 34 patients (27 men and 7 women, 67 years (range 47 - 76)) completed

the study and only these patients were used for data analyses. They were a subgroup of the 308 patients participating in the Multinational Fosinopril Efficacy and Safety Trial (FEST), conducted by the Bristol-Myers Squibb Company (17). All patients gave written informed consent and the protocol was approved by the local ethical committee. The study conforms with the guidelines of the Declaration of Helsinki. The 308 patients enrolled in the main study came from 7 countries. All participating centres were asked to deliver blood samples and relevant data on consecutive patients randomised in the main study. However, the patients enrolled in his study only came from four sites in Denmark (23 patients), two sites in Sweden (8 patients) and one site in Holland (3 patients). Demographic and clinical data are given in Table 1.

Table 1 Clinical and demographic data on the 34 congestive heart failure patients

Baseline characteristics of the patients included in the study

	Fosinopril	Placebo	
	(n = 18)	(n = 16)	
Sex (men/women)	14/4	13/3	not significant
Age (mean(s.d.))	65.7(7.3)	65.6(8.2)	not significant
Ejection fraction (mean(s.d.))	27(7)	25(8)	not significant
Systolic/diastolic blood pressure (mmHg(mean(s.d.)))	131(16)/83(13)	123(22)/82(7)	not significant
Plasma creatinine (mmol/ml(mean(s.d.)))	101(17)	113(27)	not significant
Plasma Na ⁺ (mmol/ml(mean(s.d.)))	139(3)	139(4)	not significant
Plasma endothelin (pg/ml(mean(s.d.))) at randomization	3.6(1.2)	3.5(1.3)	not significant
Furosemide/day (mg(mean(s.d.)))	125(95)	127(78)	not significant
New York Heart Association classification (II/III)	10/8	7/9	not significant
Primary cause of heart failure:			
Ischaemic heart disease	10	13	not significant
Idiopathic dilated cardiomyopathy	6	3	not significant
Valvular	2	0	not significant
Duration of heart failure (months(median(range)))	42(1-199)	41(4-204)	not significant

The patients were all treated with diuretics and 23 patients were also receiving digoxin. No patients were on any vasodilator therapy, except for 8 patients who were on treatment with nitrates due to previous symptomatic angina pectoris. A group of 21 healthy control subjects (11 men and 10 women) of mean age 46 years (range 25 - 71) were included for plasma ET reference values.

2.2. Randomization, treatment and monitoring

The patients were randomised to treatment for 12 weeks with either the ACE inhibitor, fosinopril, or placebo in a double-blinded manner. Treatment was started on 10 mg fosinopril or placebo per day and if well tolerated the dose was increased to 40 mg per day during a 2-week period. In the case of worsening heart failure requiring supplemental doses of diuretics (furosemide 40 mg/dose) for more than 2 consecutive days or more than 4 doses total, the patients were withdrawn from the study and treated with conventional therapy.

Before randomisation and at the end of study period the patients were assessed by the New York heart Association classification, a composite heart failure score (range 0 - 13, 0 = normal, 13 = severe congestive heart failure) based on degree of dyspnea, crackles, tachycardia, right heart failure and signs of congestion on chest X-ray (18), exercise test on

a bicycle ergometer in a protocol with a step of 10 watts per minute (the patient stopping at a minimum of 18 on the Borg scale) (19), left ventricular ejection fraction determined by two-dimensional echocardiography (Simpson rule) or the count-based multigated frame mode radionuclide angiography technique (20), physical examination and laboratory tests. At the end of the study the patient as well as the examining physician, who was blinded to the treatment protocol, assessed whether the patient's condition was improved, unchanged or worsened during the 12-week study period.

2.3. Blood sampling procedures and hormonal assays

Blood samples for ET analysis were taken immediately before randomization and at the end of the study. After a minimum of 15 min at rest in the horizontal position, venous blood samples (10 ml) for determination of ET were obtained in pre-cooled polyethylene tubes containing EDTA (5 · mol per ml blood) and aprotinin (540 KIU per ml blood). The samples were centrifuged immediately at 4°C and the plasma was stored at -18°C until extraction, which was performed by the use of Sep-Pak C₁₈ columns (Waters, USA). Acidified plasma was applied to the preconditioned column and the sample was eluted by the use of 3 ml of 4% acetic acid in 60% ethanol. The assay was performed as previously described (21) using a commercially available antibody (Peninsula,

USA), synthetic ET-1 and a commercially available tracer (New England Nuclear, USA). Bound antigen was separated from free antigen by the use of charcoal plasma suspension. The detection limit was less than 0,6 pg/tube ($B_0-3 \times SD$). Recovery of unlabelled ET was $81 \pm 3\%$ when 6 pg/ml were added. Results were not corrected for incomplete recovery. The interassay coefficient of variation was 9% at the level of 2,4 pg/tube. The intra-assay coefficient of variation was 11% at the level of 2,4 pg/tube.

The antibody used in this study primarily recognizes ET-1. There is a 17% cross-reactivity with human big ET and 7% cross-reactivity with ET-2 and ET-3. Thus, the term "endothelin" (ET) is used for the immunoreactivity measured as described above in relation to the applied commercially available antibody. All ET-values were expressed as picograms per millilitre (pg/ml).

2.4. Statistics

Comparison of baseline characteristics, including plasma ET levels, between the two treatment groups was performed by the two-tailed, unpaired t-test and by Fisher's exact test when comparing frequencies. Comparison within groups of the plasma ET levels before and after treatment was performed by the two-tailed, paired t-test and with the Kolmogorov-Smirnov non-parametric test when comparing the two treatment groups and healthy controls pairwise after the treatment period. This test was used because of differences in variances in the groups at the end of the study period. Simple linear correlation was used to test for a correlation between changes in plasma ET and baseline ET in the two treatment arms. The plasma ET concentrations in the different groups were tested for normal distribution. Simple and backward stepwise multiple regression analyses were done between ET values and functional parameters describing the condition of the patients, to identify characteristics possibly affecting plasma ET, between change in plasma ET and covariates that may influence alterations in plasma ET and changes in symptomatology, ejection fraction, exercise time and factors with a possible influence on that. All values are expressed as mean \pm s.d. or median (range). A P-value of $\leq 0,05$ was considered significant.

3. Results

Patients with moderately severe CHF before treatment with fosinopril had elevated plasma ET concentrations (3.5 ± 1.2 pg/ml, mean \pm s.d., $n = 34$) compared with healthy volunteers (2.0 ± 0.4 pg/ml, $n = 21$, $P < 0.0001$).

The 18 patients randomised to fosinopril treatment and the 16 patients randomised to placebo who finished this study had similar baseline plasma ET (3.6 ± 1.2 and 3.5 ± 1.3 pg/ml, respectively). We found no significant differences in baseline patient characteristics (Table 1). Treatment with fosinopril for 12 weeks reduced plasma ET to 2.5 ± 0.7 pg/ml ($P < 0.005$), in contrast to the non-significant increase in the group treated with placebo (4.3 ± 2.5 pg/ml, n.s.), so that the two groups now differed significantly ($P < 0.01$) (Fig. 1). After 12 weeks, the plasma ET level in the group treated with fosinopril had normalized ET concentrations not differing from healthy volunteers in contrast to the highly significant difference between the healthy volunteers and the placebo-treated group ($P < 0.001$) (Fig. 2). The effect of treatment with fosinopril was greatest among patients with the highest

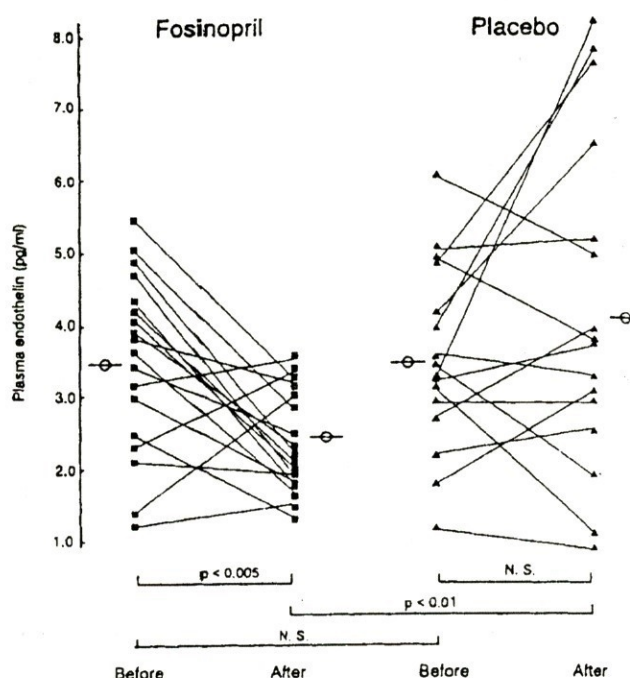


Fig. 1 - Plot of plasma ET concentration in two groups of patients before and after 12 weeks treatment with fosinopril (squares) and placebo (triangles). The 18 patients randomised to fosinopril treatment and the patients randomised to placebo who finished this study had similar baseline plasma ET (3.6 ± 1.2 and 3.5 ± 1.3 pg/ml, respectively). Treatment with fosinopril reduced plasma ET to 2.5 ± 0.7 pg/ml ($P < 0.006$) in contrast to the non-significant increase in the group treated with placebo (4.3 ± 2.5 pg/ml N.S.)

plasma ET, indicated by a significant correlation between baseline plasma ET and change in plasma ET during treatment ($r = -0.85$, $P < 0.001$). In contrast, no such correlation was found in the placebo-treated group ($r = 0.07$, n.s.). The plasma ET concentrations in the different groups fitted the normal distribution. Apart from randomization to either active treatment or placebo, only duration of heart failure turned out to be a significant covariate of factors with possible influence on alterations in plasma ET ($P < 0.001$, $\beta = 0.53$, and $P < 0.03$, $\beta = 0.35$, respectively; overall regression: $P < 0.001$, $r = 0.61$). There was no significant difference in baseline plasma ET in patients with congestive heart failure due to ischaemic heart disease or idiopathic dilated cardiomyopathy. Also, among the patients with either cause of CHF, randomised to fosinopril treatment, a similar reduction in plasma ET was demonstrated. The patients in either treatment arm who accomplished the study received a maximum of 4 doses of supplemental diuretics, equalling frusemide 40 mg/dose, during the 12-week period. One supplemental dose was given to 17 patients in the fosinopril-treated group and 13 patients in the placebo-treated group. One patient in each group received two doses of supplemental

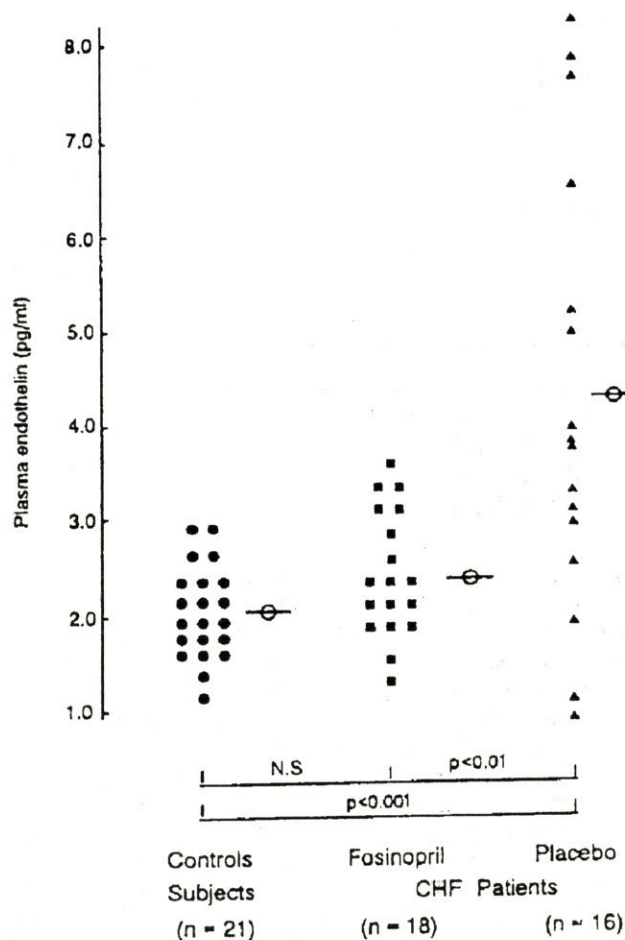


Fig. 2 - Plot of plasma ET concentration in healthy volunteers (circles), and congestive heart failure (CHF) patients treated with fosinopril (squares) or with placebo (triangles). After 12 weeks treatment the ET concentrations in the fosinopril-treated group did not differ from the healthy volunteers (N.S.). In contrast, the ET concentrations in the placebo-treated group differed significantly from both the healthy volunteers ($P < 0.001$) and the group of patients treated with fosinopril ($P < 0.01$).

diuretics and two patients in the placebo-treated group received either 3 or 4 doses (n.s.). The group of healthy volunteers was on average younger and showed a larger proportion of women than the group of CHF patients. However, in agreement with other studies [22] no correlation was found between plasma ET and age or sex among either CHF patients or healthy controls ($P = 0.13$ and $P = 0.95$; $P = 0.99$ and $P = 0.61$, respectively). At baseline the univariate regression analysis revealed that there was a significant positive correlation between plasma ET and a composite heart failure score, and a significant negative correlation between plasma ET and [1] maximum exercise test duration, [2] maximum exercise test performance, and [3] maximum

exercise test systolic blood pressure (Table 2). To verify the correlation of these functional parameters with plasma ET, a backward stepwise multiple regression analysis was performed. With this approach only the composite heart failure score and the maximum exercise test duration showed significance, giving an overall correlation of $r = 0.53$, $P < 0.001$ (Table 2). A multiple regression analysis showed that the change in plasma ET was the only covariate significantly influencing the patients' impression of improving health status during the 12-week study period ($P < 0.01$, $r = 0.5$); randomization to fosinopril or placebo almost showed significance ($P = 0.10$), but baseline dosage of diuretics or supplemental diuretics were non-significant. None of these, or other variables, explained changes in ejection fraction or bicycle exercise time during the study. However, we did find a significant correlation between subjective improving health status and increasing bicycle exercise time ($r = 0.56$, $P < 0.001$).

4. Discussion

The main findings of the present study were (i) a significant reduction of plasma ET, comparable to normal ET concentrations, after treatment with the ACE inhibitor fosinopril, and (ii) that alterations in plasma ET were mirrored in the patient's perception of health status.

The present results confirm the previously demonstrated elevated levels of plasma ET in CHF patients [3,4]. However, a large proportion of the patients in previous studies were on treatment with an ACE inhibitor, making an evaluation of the effect of this therapy on plasma ET impossible. Whether the potent vasoconstrictor activity of ET plays a contributing role in the increased vascular resistance noted in heart failure is unknown. Long-term treatment with ACE inhibitors reduces peripheral resistance in CHF [23]. However, the mechanisms underlying the vasodilatory effects of ACE inhibitors are not fully understood, but there is evidence that angiotensin II stimulates expression of ET mRNA [1,13]. Thus, despite the fact that ACE inhibitors only partially block angiotensin II formation, ET transcription and translation may be suppressed, thereby making reduced ET formation a likely contributing vasodilatory mechanism.

The present study is the first to demonstrate that long-term treatment with an ACE inhibitor (fosinopril) lowers plasma ET in moderately severe CHF to normal levels. This is in contrast to another study [24] in which intravenous infusion of enalaprilat for 2h in patients with intractable heart failure produced only a transient fall in plasma ET during the initial 10 min, whereafter plasma ET concentration returned to baseline values. On a long-term basis, Rousseau et al. [25] showed almost twice the plasma ET in patients with New York Heart Association (NYHA) classification II or III despite treatment with enalaprilat for an average of 14-42 months (range 14-60). However, no baseline plasma ET values were available in this study. One single previous study [26] found no change in plasma ET after 16 weeks of treatment with either the ACE inhibitor captopril or quinapril in patients with CHF. The reasons for the difference in effect on plasma ET may include one of the following. The patients in the study by Townsend et al. [26] belonged to NYHA classes III and IV, had a slightly lower ejection fraction and were on average 5 years younger than the patients in our study. However, we did not find any relation between the effect of

Table 2 Simple and multiple regression analyses of plasma endothelin against functional parameters in 34 patients with moderately severe congestive heart failure

Simple regression analysis		
Endothelin vs.	<i>r</i>	<i>P</i> -level
Composite heart failure score	0.39	< 0.01
Maximum exercise test duration	-0.38	< 0.01
Maximum exercise test performance	-0.39	< 0.01
Maximum exercise systolic blood pressure	-0.32	< 0.05

Stepwise multiple regression analysis		
Overall regression equation: Intercept coefficient = 5.56, <i>r</i> = 0.53, <i>F</i> -test = 7.88, <i>P</i> < 0.001		
Variable	B-coefficient (± s.e.)	<i>P</i> -level
Composite heart failure score	0.35 (0.13)	< 0.01
Maximum exercise test duration	-0.35 (0.13)	< 0.01

treatment with fosinopril and NYHA class, ejection fraction or age. More important may be the use of different ACE inhibitors used in the different studies. Fosinopril contains a phosphorus atom in contrast to other ACE inhibitors. It is important for binding to the angiotensin-converting enzyme (16). Phosphoramidon is a phosphorus-containing inhibitor of the ET-converting enzyme that converts the almost inactive big ET into ET I. [27] The phosphorus atom is an absolute requirement for the inhibiting effect of phosphoramidon. Whether the phosphorus atom in fosinopril may lead to an inhibition of the ET-converting enzyme is unknown. It has also been demonstrated that captopril has no inhibiting effect on the ET-converting enzyme [28]. The earlier studies were conducted without a parallel placebo-treated group. This reduced the chance of detecting the ACE inhibitor's ability to delay rather than possibly improve symptoms of heart failure. Also, the maximum dosage in the study by Townend et al. [26] was reached shortly before the end of study for the patients treated with captopril, and 4 weeks before end of study for the patients treated with quinapril. In our investigation the maximum dosage was reached after 2 weeks of treatment, which was 10 weeks before the end of the study. Supporting the likelihood of this explanation was that plasma norepinephrine was unchanged during treatment with quinapril, despite improvement in the exercise test and hemodynamic parameters [29]. Other studies give good evidence for the sympatholytical effect of ACE inhibitors in CHF [8].

We found the alterations in plasma ET to be the only covariate explaining changes in the patients' impression of health status. This indicates that a rise or fall in plasma ET in CHF possibly affects the symptomatology of the disease. It is well documented that plasma ET increases with the progression of CHF (3,6) and appears to play an important role in the pulmonary circulation [5]. We also found a strong positive correlation between plasma ET and a composite heart failure score classification and a negative correlation between plasma ET and maximum exercise test duration. Therefore it may be of clinical importance that there was a highly significant correlation between baseline plasma ET and changes in plasma ET during treatment with fosinopril, indicating the greater effect of treatment among patients with the highest plasma ET.

ACE inhibitors exert their actions by a vasodilatory effect,

normalization of peripheral structural changes [7]. An improvement in skeletal muscle blood flow [23], and possibly normalization of endothelial dysfunction [30]. As demonstrated in the present study, plasma ET is reduced after treatment with the ACE inhibitor, fosinopril and both baseline concentrations as well as changes in plasma ET are expressed in the clinical severity of CHF. In addition, experimental data suggest that the vasodilatory effect, and possibly the antiproliferative effect, of an ACE inhibitor may in part be explained by an inhibitory effect on ET release [14]. It is well established that patients following cardiac transplantation have systemic hypertension, characterized by elevated systemic resistance, despite a normalization of other neurohormonal abnormalities [31] except for circulating ET, which is further elevated in plasma after cardiac transplantation [32]. Finally, treatment with recently developed ET receptor blockers and ET-converting enzyme inhibitors in heart failure patients on full conventional therapy resulted in additional arterial vasodilatation [33], improved cardiac index, and decreased systemic and pulmonary vascular resistance [34]. Thus, it seems that circulating ET plays a more direct pathophysiological role in CHF than being a mere marker of the disease.

In conclusion, the present study demonstrates for the first time that treatment with the ACE inhibitor, fosinopril, reduces and normalizes the elevated plasma ET levels in CHF, with the greatest effect in patients with the highest plasma ET. This indicates another possible mechanism for the vasodilatory action of ACE inhibitors. In addition, a direct inverse correlation between plasma ET concentrations and clinical parameters was demonstrated. Finally, a sensation of alterations in health status was correlated to changes in plasma ET, perhaps suggesting that ET may play a role in the development of symptoms with the progression of CHF.

The present investigation confirms and extends previous investigations regarding ET in CHF and documents the influence of the well-established ACE inhibitor treatment on plasma ET in CHF.

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SPITALUL CLINIC CENTRAL DE COPII "GRIGORE ALEXANDRESCU"

Departamentul de Toxicologie Clinică

TOXAPEL



Un serviciu telefonic de urgență pentru intoxicații la copil

- Toxapel este un serviciu telefonic de urgență realizat de departamentul de toxicologie al Spitalului Clinic Central de Copii "Grigore Alexandrescu" București și este destinat informării asupra modului în care trebuie acordat primul ajutor unui copil intoxicat până la sosirea salvării sau până la prezentarea la spital
- TOXAPEL - funcționează 24 de ore din 24
- poate fi apelat de la orice post telefonic fix, mobil sau public
- lucrează ca voluntari medicii și asistentele din serviciul de toxicologie
- Baza de date computerizată cuprinde toate substanțele medicamentoase înregistrate în România, precum și alte substanțe cu potențial toxic utilizate în industrie și gospodărie, precum și netoxice, totalizând aproximativ 5000 de înregistrări. Asociat fiecărui toxic există un protocol de acordare a primului ajutor.

Cine are nevoie de TOXAPEL?

Toți părinții, bunicii, toți adulții, medicii de familie ce au în apropiere un copil care s-a intoxicat cu un medicament, o substanță chimică, a ingerat sodă caustică, acizi, etc.

NU uitați! Prima jumătate de oră este esențială în cazul celor mai multe intoxicații. Tratamentul de urgență pe care vi-l vor indica specialiștii noștri va determina o însănătoșire mult mai rapidă decât un tratament efectuat după două ore de către un specialist.

Telefoane:

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