

ROLE OF ANGIOTENSIN CONVERTING ENZYME (ACE) INHIBITORS IN HYPERTENSION AND CARDIOVASCULAR PROTECTION MANAGEMENT

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Abstract

Angiotensin converting enzyme (ACE) inhibitors plays an important role in hypertension and cardiovascular protection management, both alone and in various combinations with other pharmacological agents from different classes. This position is supported by the significant hemodynamic, cardiac effect, renal effect, antithrombotic and neurohormonal effects of these pharmacological agents, effects demonstrated in clinical trials with a significant number of patients analysed. ACE inhibitors have proven their efficacy and safety in blood pressure control, as well as a substantial influence in reducing cardiovascular risk, at the same time having target organ protection. The main result of ACE inhibitors therapy is to improve quality of life and reduce cardiovascular morbidity and mortality.

Rezumat

Inhibitorii enzimei de conversie a angiotensinei (IECA) ocupă un rol important în managementul HTA (hipertensiunii arteriale) și protecției cardiovasculare, atât în monoterapie cât și în diverse combinații cu alte medicamente din diferite clase farmacologice. Această poziție este susținută de importantele efecte hemodinamice, cardiace, renale, antitrombotice și neurohormonale ale acestor agenți farmacologici, efecte demonstrate în cadrul unor studii clinice cu număr semnificativ de pacienți analizați. IECA și-au dovedit eficiența și siguranța în controlul valorilor tensionale, precum și o influență semnificativă în reducerea riscului cardiovascular global, alături de protejarea organelor țintă. Rezultatul principal al terapiei cu IECA este ameliorarea calității vieții pacienților și reducerea mortalității și morbidității de cauze cardiovasculare.

Keywords: ACE inhibitors, arterial hypertension, cardiovascular risk.

Introduction

The cardiovascular pathology damages the quality of patient's life, in all respects. The identification of the most favourable therapy, personalized and providing good compliance are important aims for each clinician [28].

The inhibitors of angiotensin converting enzyme I represent a group of first-line drugs used in the treatment of hypertension, in the treatment of heart failure, and of the patients with myocardial infarction, both in the early phase of the disease and in the long-term treatment of ischemic heart disease. It also became increasingly clear the cardiovascular preventive role, their administration in high risk patients resulted in decreased mortality risks, decreased risks of vascular accidents and myocardial infarction [5].

ACE inhibitors have the basic structure of 2-methyl-propyl-L-proline; they are classified into three types, chemically different depending on the ligand group of the zinc ion: sulfhydryl, carboxyle and phosphoryl. These structures affect directly tissue distribution and elimination pathways [16]. Important to note is that ACE inhibitors do not inhibit the actions of angiotensin II (AT II) mediated by the activation of AT1 and AT2 receptors and do not interact directly with other components of the renin angiotensin aldosterone system (RAAS) [14]. ACE inhibitors also reduce the secretion of aldosterone and vasopressin.

ACEI pharmacokinetics – the absorption varies widely within the ACEI class, from 25 % to 75 %. Most ACE inhibitors are prodrugs, esters of active compounds. They remain inactive until they are converted to active compounds by hydrolysis in the liver or gastrointestinal tissue, compounds with increased fat solubility in order to be absorbed more quickly and completely. The varying degrees of binding to ACE, the access to target tissues and elimination pattern demonstrate why the large differences in bioavailability have an almost uniform clinical expression [30].

The main route of elimination of ACEI is the renal one, except for zofenopril, spirapril, trandolapril and fosinopril which have significant liver elimination.

Pharmacodynamics of ACEI - ACEI pharmacodynamic profile can be assessed from various perspectives: changes in blood levels of ACE, AT I, AT II and renin, hemodynamic changes. The obvious mechanism of action is the marked reduction in circulating levels of AT II, preventing direct vasoconstriction induced by this peptide. Simultaneously, ACE is inhibited apparently variably in the vascular walls and other tissues, including the brain and the heart. Pharmacological blockade of plasma ACE appears to be less important in chronic treatment, whereas the inhibition in

various tissues appears to be the main determinant of the pharmacological effects of the ACE inhibitors. Additionally, ACE inhibitors inhibit kininase II and increase bradykinin levels, stimulating the release of nitric oxide and vasoactive prostaglandins [12].

Research on understanding the mechanisms by which ACE inhibitors decrease blood pressure (BP) and produce multiple effects continues to expand [33]. The antihypertensive effect of ACE inhibitors is the result of the contribution of different mechanisms, other than reducing the levels of AT II: decreased aldosterone retention (followed by natriuresis and reduction of renal sodium reactive retention); attenuation of the expected increase of sympathetic nervous system (SNS) activity, typically observed after vasodilation; suppression of endogenous endothelin secretion [7]; improvement of endothelial dysfunction [19].

Hemodynamic effects - ACEI decrease total peripheral vascular resistance without significant changes in the frequency and cardiac output, pulmonary capillary pressure and circulatory vegetative reflexes; renal blood flow increases, glomerular filtration is not influenced in any way and cerebral blood flow is maintained; ACE inhibition results in the attenuated reflectivity of the pressure wave and increased aortic distensibility [25]. These haemodynamic improvements contribute to the regression of hypertrophy, both in the heart and the vasculature, which may be quantitatively superior to those observed in the case of other antihypertensive agents [25]. In normotensive or hypertensive patients without heart failure, ACE inhibitors affect capillary pressure and the effect may be responsible for their ability to reduce the swelling of the ankle observed in patients receiving calcium channel blockers, where the two agents are associated [9]. Moreover, they reduce the pressure from the right atrium and the left ventricle and the pulmonary arterial pressure. They develop large artery compliance, protecting vessels against the trauma caused by hypertension. ACE inhibitors administered alone control blood pressure values in 50% of hypertensive patients, and by adding a loop or thiazide diuretic to the therapeutic scheme, the results can exceed to 75%.

Cardiac effects - ACEI provide multiple benefits on the heart:

- left ventricular hypertrophy (LVH) regression, increased reserve of coronary flow [21], attenuation of coronary vasoconstriction mediated sympathetically and relief of angina in some patients [2], prevention of nitrate tolerance, reduced post-AMI (acute myocardial infarction) mortality, reducing mortality and morbidity in patients with left ventricular systolic dysfunction, diabetes or cardiovascular risk, independently of the reduction

in blood pressure. It can be used safely in patients presenting aortic stenosis, enhancer factor of total cardiovascular risk [3].

– improving acute and chronic congestive heart failure by altering remodelling and sustained reduction in preload and afterload; in patients with LV systolic dysfunction or cardiac insufficiency (CI), ACE inhibitors have been shown to be effective in halting the progression of heart dilation for a long period of time [10].

– the inhibition of atherosclerosis [26]; long-term treatment with ACE inhibitors delay the progression of carotid atherosclerosis in patients with vascular damage or diabetes but without heart failure or left ventricular dysfunction [18].

Neurohormonal effects - short-term treatment with ACE inhibitors decreases aldosterone levels and increased renin release and AT I level [29]. In the long term administration of ACE inhibitors, AT II and aldosterone both tend to return to baseline levels by the activation of other pathophysiological mechanisms such as the phenomenon of "aldosterone escape" [24].

Renal effects - ACEI decrease renal vascular resistance, increase renal blood flow and promote the excretion of Na⁺ and water. Glomerular filtration rate remains unchanged or decreases very slightly. ACE inhibitors prevent the progression of microalbuminuria, attenuate progression of renal failure in patients with varied non-diabetic nephropathy and provide renoprotection in those with diabetes.

Research results on ACEI treatment in patients with cardiovascular damage

ACCEPT study aimed to assess the efficacy and safety of quinapril in hypertension [1]. The 3742 patients with an average age of 56 years and average duration of hypertension for five years, received a therapeutic regimen of quinapril, the initial dose being 10 mg per day. The titration of blood pressure (BP) response was performed most frequently at intervals of two weeks, with the possibility of doubling the dose, reaching the maintenance dose of 10-20 mg per day, without exceeding 40 mg per day. The follow-up period was 6 months. Results revealed that out of 2979 patients treated with quinapril, after 3 months there were stabilized 77 %; out of 2517 patients treated with quinapril, after 6 months there were stabilized 84 %. The response to quinapril was similar in patients newly diagnosed and in patients with a hypertensive history. Adverse events were reported in 980 patients (26.2%), most commonly cough, clearly correlated with quinapril in 3.6% of cases and serious adverse effects in 55 patients (1.5 %).

CAPPP study investigated whether antihypertensive treatment with captopril reduces mortality and cardiovascular morbidity more than a regimen that does not include an ACEI [11]. The 10,800 selected patients, aged between 25 and 66 years, with a minimum diastolic blood pressure (DBP) of 100 mm Hg (no upper limit), were monitored over a period of five years. The captopril regimen was 50 mg per day, possibly 100 mg daily if DBP exceeded 90 mm Hg, with the possibility of associating other antihypertensive drugs, diuretics by choice. The results indicate that the incidence of fatal and non -fatal myocardial infarction (MI), CVA [27] (cerebral vascular accident) and other cardiovascular death in the captopril group were similar to conventional groups, that is, 11.1/1000 patient- year *versus* 10.2/1,000 patients, relative risk 1.05, $p = 0.52$. Cardiovascular mortality was lower with captopril than with conventional therapy (76 vs. 95 events, hazard ratio 0.77; $p = 0.092$) and the incidence of stroke (CVA) was higher with captopril (189 vs. 148 events, hazard ratio 1, 25, $p = 0.044$).

With regard to stroke prevention, metaanalyses BPLTTC (Blood Pressure Lowering Treatment Trialists Collaborative - 2003), which brought together 29 randomized studies, controlled on a number of 162 341 patients with an average follow-up from 2 to 8 years, have shown that the use of ACE inhibitors reduce the risk by 28 % as compared to placebo [35].

CARE study aimed at confirming the effectiveness and safety of ramipril in real world conditions [15]. The 11,100 patients with the average age of 55.7 years, with mild to moderate hypertension, were administrated ramipril from 2.5 to 10 mg per day over a period of 8 weeks.

Results: In patients with systolic - diastolic hypertension, ramipril decreased BP (blood pressure) from 167/102 to 146/89 mm Hg ($p < 0.0001$). The highest response rate (87 %) was recorded in the elderly and the lowest (81 %) in black patients. In patients with isolated systolic hypertension ramipril reduced sanguine blood pressure (SBP) from 167 /85 to 149/82 mm Hg ($p < 0.0001$). These patients had a lower response rate, 72 % for white patients and 64 % for black patients. Of the 13 % adverse effects reported, 81 % seem to be correlated with the treatment. The most common side effects were cough (3%), headache (2.4%) and dizziness (1.8 %).

PREMIER study -double-blind, randomized, over a period of one year, which evaluated the effect of the fixed combination NoliprelArg[®] (perindopril arginine + indapamide) *versus* enalapril on the rate of urinary albumin excretion in 457 hypertensive patients with type 2 diabetes and albuminuria (> 20 and < 500 mg / mg) [20]. The results indicated that this fixed combination is effective in reducing blood pressure, the rate of urinary albumin excretion and in improving renal perfusion.

HYCAR and DIAB-HYCAR studies test the hypothesis whether ACE inhibition with daily small dose of ramipril, which has no significant effect on BP (blood pressure), can reduce cardiovascular morbidity and/or mortality in non-insulin diabetic normotensive or hypertensive patients with persistent albuminuria and to assess the effect of ramipril on left ventricular hypertrophy (LVH) and BP (blood pressure) in hypertensive patients treated with furosemide 20 mg daily [13]. The 115 patients (75 R, 40 placebo) and hypertension and LVM (left ventricle mass) $> 120 \text{ g / m}^2$ (male) and $> 98 \text{ g/m}^2$ (female) received from 1.25 to 5 mg ramipril once a day or placebo over a period of six months. Study results revealed the following: after six months, LVM increased by $9 \pm 8 \text{ g}$ in the placebo group and decreased by $13 \pm 8 \text{ g}$ ($p = 0.04$ versus Placebo) and $20 \pm 7 \text{ g}$ ($p = 0.004$ vs. placebo) in the groups receiving 1.25 and, respectively, 5 mg of ramipril.

PREAMI study showed that the treatment with perindopril significantly reduces the risk of death, hospitalization for heart failure and vascular remodelling in elderly patients after myocardial infarction with preserved left ventricular function [22].

RACE study aimed to compare the effects of ramipril and atenolol on left ventricular hypertrophy (LVH) and BP blood pressure (BP) in patients with hypertension [23]. The 193 patients, aged between 27 and 72 years with mild to moderate hypertension were monitored over a period of six months. The therapeutic regimen consisted of ramipril, in a dose of 2.5 mg once a day or atenolol 50 mg once a day; if blood pressure (BP) has proved non-satisfactory, the initial dose was doubled after two weeks, and after further two weeks, a diuretic was associated to uncontrolled patients. The results showed that the SBP and DBP decreased significantly in similar degrees by both treatments. Cardiac frequency (CF) was significantly reduced only in the group treated with atenolol. LVM was significantly reduced in the ramipril group (-11 % after 6 months) as compared to the group treated with atenolol which decreased only slightly; adverse effects were reported in 6 patients in the ramipril group and 8 patients in the atenolol group.

Other researches have also shown the benefits of associating the selective beta-blockers in the treatment of the patients suffering of hypertension associated with coronary disease and other risk factors [8].

ACCOMPLISH study demonstrated that the therapeutic regimen resulted from the combination of an ACE inhibitor (benazepril) with calcium canal antagonists (amlodipine) reduce more effectively cardiovascular morbidity and mortality and the progression of nephropathy

compared to the combined treatment ACE + thiazide diuretic therapy (hydrochlorothiazide) [4].

ANBP2 Study (2003) - prospective, randomized, open study which included 6083 hypertensive subjects (Australia) aged between 65 and 84 years, compared ACE inhibitors (enalapril) with a diuretic in reducing blood pressure and preventing cardiovascular diseases [34]. The results showed a similar decrease in the level of blood pressure in both groups, but regarding the reduction of the risk of cardiovascular event, ACE inhibitors have proved more effective (the risk was reduced by 11%, more pronounced in men than in women). The rate of non-fatal cardiovascular events and MI were also reduced in the group treated with ACE inhibitors.

EUROPA Study - multicentred, randomized, double blind, placebo controlled study, applied to 12 218 patients with an average age of 65 years that monitored the revelation of long term effects (3-4 years) of perindopril in reducing cardiovascular events in patients with stable coronary disease, without apparent heart failure [31]. The results showed a risk reduction of 20% under perindopril treatment.

HOPE Study – the study was initiated to determine the role of ACE inhibitors and vitamin E in patients at high risk of cardiovascular events, but did not have left ventricular dysfunction or heart failure [32]. High-risk patients who were more than 55 years old, with evident vascular disease or diabetes plus another cardiovascular risk factor (hypertension, dyslipidemia, microalbuminuria) and who were not aware of having low ejection fraction or heart failure were eligible to participate in the study. The average follow-up period was 4.5 years. Stroke incidence was reduced by 32 % with ramipril, AMI by 20% and cardiovascular death by 25%.

Conclusions

The main goal of the treatment with ACE inhibitors is to improve the quality of life and to reduce mortality and morbidity from cardiovascular causes. ACE inhibitors have proven being effective both in lowering blood pressure and in preventing complications and organ protection, either alone or in various combination regimens with other antihypertensive pharmacological agents. Although they have been developed as antihypertensive drug substances, they showed their effectiveness and usefulness in other conditions such as congestive heart failure, myocardial infarction, atherosclerotic vascular disease, diabetic nephropathy.

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