PHARMACOLOGICAL ANTAGONISATION OF RENIN-ANGIOTENSIN-ALDOSTERONE SYSTEM (RAAS)

MARILENA MONICA ŢÂNŢU[1]

[1]*PhD candidate University of Medicine and Pharmacy, Craiova*

Keywords: *renin-angiotensin-aldosterone system (RAAS), neurohormonal, pharmacological*

Abstract: *The renin-angiotensin-aldosterone system (RAAS) is a complex neurohormonal system, essential in regulating blood pressure and maintaining fluid and electrolyte balance and with an important influence on cardiovascular structure and function components. RAAS complexity, as a neurohormonal system, determines the existence of multiple ways to discontinue the pharmacological activity, intervening at different levels, depending on the constituent element to which the pharmacological agent is addressed or on the enzymatic reaction that is meant to be inhibited.*

Cuvinte cheie: *sistemul renină-angiotensină-aldosteron (SRAA), neurohormonal, farmacologic*

Rezumat: *SRAA este un sistem neurohormonal complex, cu rol esenţial în reglarea presiunii arteriale şi menţinerea echilibrului hidro-electrolitic şi cu influenţă importantă asupra structurii şi funcţionalităţii componentelor aparatului cardiovascular. Complexitatea SRAA ca sistem neurohormonal determină existenţa a multiple căi de a întrerupe farmacologic activitatea sa, intervenind la diferite nivele, în funcţie de elementul constitutiv caruia se adreseaza agentul farmacologic sau de reacţia enzimatică ce se doreşte a fi inhibată*

RAAS complexity as a neurohormonal system determines the existence of multiple pathways (1) to pharmacologically discontinue its activity, intervening at different levels, depending on which constituent agent is addressed to or on the enzymatic reaction that is meant to be inhibited:

- the first path, widely used, refers to the use of β-blockers in order to reduce the release of renin from the juxtaglomerular cells;
- the second way, the direct inhibition of renin activity is actively investigated with different renin inhibitors, such as aliskiren; the direct inhibition of RAAS at this level offers an alternative for lowering the blood pressure (BP) and for organs protection. In addition, there are assumptions that the renin inhibitors act synergistically with other inhibitors of RAAS, optimizing the pharmacological suppression of RAAS.(2) Direct renin inhibition could be achieved through passive or active immunization with anti-renin polyclonal antibody production.(3)
- the third way is to inhibit ACE (angiotensin converting enzyme) activity - the enzyme that converts angiotensin I (AT I) inactive decapeptide in the angiotensin II (AT II) potent hormone – with agents called angiotensin converting enzyme, confirmed by the rapid increase of the therapeutic use;
- the fourth way is the competitive antagonism by attachment to AT II receptors, without inducing its cellular effects; administration of AT1 receptor selective blocker in the patients with cardiovascular disease has resulted in increasing the level of AT II.(4) Under the inhibition of AT1 receptor, the excess of AT II may have beneficial therapeutic results, either by the selective stimulation of cardiac AT2 receptor, or by accelerating the transformation of AT II in angiotensin (1-7), with its increase.(5) Studies have shown that blocking the AT1 receptor with Olmesartan reduced cardiac hypertrophy induced by myocardial infarction and improved ventricular contractility. Furthermore, olmesartan brought about the increased plasma concentrations concomitantly with the increase of RNA_m expression of ACE 2 in the myocardium.(6) Due to the fact that the action of the angiotensin II is mainly mediated by type 1 receptors, by their blocking, we antagonise the peptide effects: rapid and slow pressure effect, stimulation of the peripheral sympathetic system, CNS effects (thirst, antidiuretic hormone (ADH) release, increased sympathetic tone) release of adrenaline by medulosuprarenal, stimulation of aldosterone secretion, renal effects, hypertrophied cardiovascular effects.(7) Angiotensin blockers receptors (ARB) have clear advantages over the ACE inhibitors, materialized in the marked reduction of the side effects, especially of cough and angioedema. Cough is considered the result of bradykinin accumulation after the inhibition of the conversion. Bradykinin has numerous beneficial effects: vasodilation, antiplatelet effects, endothelial protection and certain side effects: angioedema, possible arrhythmias. One thing is worth noting, the fact that after blocking the AT1 receptor, AT2 subtype remains active and works through an unknown mechanism, leading to the formation of bradykinin (8), with its mentioned above effects. It is considered that AT1 receptor blockers lead to a reduced genesis of bradykinin and to a reduced endothelial protection.

AT1 receptor blockers used in practice are losartan, candesartan, irbesartan, valsartan, telmisartan, eprosartan. Losartan shows a 33% bioavailability after oral administration

[1]Corresponding author: Monica Ţânţu, Muntenia Medical Hospital, Str. Pictor Nicolae Grigorescu, Nr. 2A, Piteşti, România, e-mail: tantumonica@yahoo.com
Article received on 28.11.2011 and accepted for publication on 31.03.2012
ACTA MEDICA TRANSILVANICA June 2012;2(2):207-210

and the half-life is of 2 hours. Metabolism is achieved by oxidation. One of the metabolites, 5-carboxylate derivative blocks more intensely the AT1 receptors and has a longer half-life: 6-9 hours. These features recommend it as being responsible for the effect of losartan. The elimination is renal, partially under its unmetabolized part. Iberartan and Valsartan have a stronger action on AT1 receptors and are better tolerated. RAAS blocking at ACE level or at the level of the AT1 receptor provides real benefits for heart and kidneys.(9) ACE and ARB associated therapy protects the metabolic syndrome and prevents atrial fibrillation, while ARB shows real benefits in the hypotensive therapy, especially by the regression of blood pressure values in hypertension associated with target organ damage.

- the fifth way is to antagonize the mineralocorticoid receptors; pharmacological blockage at this level leads to the improvement of the endothelial dysfunction, modulates inflammatory the inflammatory mechanisms between blood and the vascular walls, reduces cell proliferation and cardiovascular remodelling, bringing about to cardiovascular damages of different degrees of severity;(11) the best known antialdosteronic drugs are eplerenone and spironolactone. Research has shown that the mineralocorticoid blocking receptors affect the balance between ACE and ACE 2, that is they decrease ACE and increase ACE 2, with the reduction of AT II level, suggesting a feedback control.(12) Mineralocorticoids cause salt and water retention and increase the excretion of K^+ and H^+ by binding to specific mineralocorticoid receptors. Class prototype is 17-spironolactone. Like other diuretics retaining K^+, spironolactone is often administered together with thiazide or loop diuretics to treat oedema and hypertension. Such combinations result in increased mobilization of oedema fluid without perturbations of K + homeostasis. Spironolactone is particularly useful in the treatment of primary hyperaldosteronism (adrenal adenoma or bilateral adrenal hyperplasia), as well as in refractory oedema associated with secondary aldosteronism (IC, cirrhosis, nephrotic syndrome, severe ascites). Spironolactone is considered the diuretic of choice in the patients with liver cirrhosis. Spironolactone added to the standard therapy significantly reduces morbidity and mortality in the patients with heart failure – New York Heart Assosication (NYHA) functional classes III and IV. The RALES study suggests that the beneficial effects of spironolactone are additive to those of ACEs.Another mineralocorticoid receptor antagonist, extensively investigated is Eplerenone (EPHESUS-Eplerenone versus placebo in the patients with systolic dysfunction after myocardial infarction; EMPHASIS-Eplerenone versus placebo in the patients with class II heart failure and ejection fraction of no more than 35%).

Angiotensin converting enzyme inhibitors (ACEI)

ACE inhibitors have in their basic structure 2-methyl-propyl-L-proline, are classified in three categories, chemically different, depending on the zinc ion ligand group: sulphidril, carboxyl and phosphoryl. These structures directly affects the tissue distribution and elimination pathways (17), differences that can alter their effects on various organ functions beyond their ability to lower blood pressure by blocking the conversion of AT I to AT II, reducing its circulating and local levels. It is important to note that ACE inhibitors do not inhibit the actions of AT II mediated by the activation of AT1 and AT2 and it does not directly interact with other components of RAAS.(15) ACE inhibitors also reduce the secretion of aldosterone and vasopressin.

Pharmacological profile of ACE

The pharmacokinetics of ACE - absorption varies widely in ACE class, from 25% to 75%. Most of ACE inhibitors are prodrugs, esters of the active compounds. They remain inactive until converted into active compounds by hydrolysis in the liver or gastrointestinal tissue, increased fat solubility compounds being absorbed more quickly and completely. The variable degrees of binding to ACE the access to target tissues and elimination demonstrate why the large differences in bioavailability have an almost uniform clinical expression.

The main route of eliminating ACEs is renal, except for zofenopril, spirapril, trandolapril and fosinopril having significant hepatic elimination. Captopril is eliminated from the body the fastest, with a duration of action of 6 hours, while ramiprilat and trandolaprilat (the active metabolite of ramipril, of trandolapril, respectively) are excreted the slowest compared to other ACE inhibitors. Fosinopril is balanced regarding the way of excretion; in the presence of impaired renal function the elimination by the liver gradually increases and thus, it does not require dose adjustment. In fact, this is true for all ACE inhibitors previously mentioned which also have hepatic route of elimination.

The pharmacodynamics of ACE - ACE pharmacodynamic profile may be appreciated by 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 of the circulating levels of AT II, preventing direct vasoconstriction induced by this peptide. Simultaneously, ACE is inhibited apparently variable at the level of the vascular walls and of other tissues, including the brain and the heart. Pharmacological blocking of serum ACE seems to be less important in the chronic treatment, whereas inhibition in different tissues occurs as the main determinant of the pharmacological effects of ACE inhibitors. In addition, ACE inhibitors inhibit kininase II and increase bradykinin levels, stimulating the release of nitric oxide and vasoactive prostaglandins.(17)

Research on understanding the mechanisms by which ACE inhibitors reduce PB and produce multiple effects and is ongoing.(18) The antihypertensive effect of ACE inhibitors is the result of the contribution of different mechanisms, and of others than the reduction of AT II levels:

• decreased aldosterone retention, which can cause renal sodium retention and the reduction of natriuresis along with the reduction of BP;

• attenuation of the expected increase in sympathetic nervous system (SNS) activity, typically occurring after vasodilation (cardiac output does not increase, as happens with the direct vasodilators, such as hydralazine);

• suppression of the endogenous endothelin secretion and;

• improvement of endothelial dysfunction.

Effects of ACE

Hemodynamic effects - ACE inhibitors reduce total peripheral vascular resistance without significant changes in the rate and cardiac output, pulmonary capillary pressure and circulatory autonomic reflexes, increased renal blood flow; glomerular filtration is not influenced and the cerebral blood flow is maintained; ACE inhibitors have as a result the attenuation of the arterial wave reflection and increased aortic distensibility. These hemodynamic improvements contribute to the regression of hypertrophy, both at heart at vascular level, regression that can be: quantitatively superior to those achieved with other antihypertensive agents.(22) In the normotensive or hypertensive patients without heart failure, ACE inhibitors affect the postload and capillary pressure; they are also

venodilatators and their effect may be responsible for their ability to reduce ankle swelling observed in the patients treated with calcium channel blockers, when two agents are associated.(23) Furthermore, they reduced the pressure in the right atrium and left ventricle, as well as the pulmonary arterial pressure. They increase compliance of the large arteries, protecting the vessels from consecutive high trauma.

Cardiac effects - ACE provides multiple benefits on the heart :

• LVH regression, to a greater extent than that obtained with other classes of drugs;

• increase in coronary flow reserve;

•attenuation of the coronary vasoconstriction mediated sympathetically and the relief of angina in some patients;(25) Survival and Ventricular Enlargement (SAVE) and studies of left ventricular dysfunction (SOLVED) studies have shown that ACE inhibitors reduce by 20-25% the risk for unstable angina and acute myocardial infarct (AMI) in the patients with left ventricular dysfunction and congestive heart failure.(26,27)

• prevention of nitrate tolerance is smilingly the best done with captopril;

• reducing mortality after AMI, more obviously in the patients with heart failure; but probably in all high-risk patients;(28) ACE inhibitors have a favourable effect on reducing mortality and morbidity in the patients with left ventricular systolic dysfunction, diabetes or cardiovascular risk independently of blood pressure reduction. They can be used safely in patients presenting aortic stenosis, which is a total cardiovascular risk factor potent.

• improving the acute and chronic congestive heart failure by altering remodelling and by sustained reduction in preload and postload, the first therapeutic class that has been shown to halt the progression of remodelling thus, reducing morbidity and mortality in heart failure are the ACE inhibitors. ACE inhibition has as a result both the decrease of circulating and local AT II and the BK increase. Consequently, the balance between the remodelling process (AT II) and anti-remodelling (BK) are beneficially in favour to the latter.

ACE inhibitors prevent the experimental remodelling such as the increase of the myocardial mass away from the affected region, induced by transmyocardial electric shock.(30) Please note that this effect is lost when administered antagonists of BK B2 receptor specific, suggesting the predominance of BK-related effect.

In clinical studies, in the patients with LV systolic dysfunction or HF (heart failure) ACE inhibitors have proved effective in stopping the progression of cardiac dilatation for a long time.(31) On the contrary, in patients not receiving ACE inhibitors, cardiac volumes continued to grow. Such studies are, in fact, subgroup analysis of prospective studies of large groups, and showed that the beneficial effect on remodelling is accompanied by the CV improvement and reduced mortality in patients with HF.(32)

• on animal models, inhibition of atherosclerosis (33), even without affecting plasma lipid levels or PS; the antiaterogenic properties can be attributed to the inhibition of formation of AT II, bradykinin potentiation and increased nitric oxide (NO) release, resulting in the reduction of migration and proliferation of the vascular smooth cells, accumulation and activation of the inflammatory cells, oxidative stress and improving the endothelial function.(34) SECURE study, a substudy of HOPE, showed that long-term treatment with ACE inhibitors slow the progression of carotid atherosclerosis in the patients with severe vascular damage or diabetes but without heart failure or left ventricular dysfunction.

Neurohormonal effects - short-term treatment with ACE inhibitors determines the decrease of the aldosterone level and the increase of the rennin release and of the AT1 level.(36) In addition, ACE inhibitors reduce plasma levels of epinephrine, norepinephrine and vasopressin. Increased AT I level is focused on enhancing the production of bradykinin and the synthesis of AT II by ACE unmediated mechanism. The long term administration of ACE inhibitors, both AT II and aldosterone tend to return to the baseline levels through the activation of other pathophysiological mechanisms, such as the of "aldosterone escape" phenomenon.(37)

Renal effects - ACE inhibitors reduce renal vascular resistance, increase the 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 the progression of renal failure in the patients with various non-diabetic renal disease and provides renoprotection in the patients with diabetes.

ACE inhibitors and their antithrombotic effect

Angiotensin II induces platelet activation and stimulates their aggregation, therefore blocking the actions of angiotensin II by ACE or ARB administration, we obtain a direct antiplatelet effect.(39) Angiotensin converting enzyme inhibitors influence the process of thrombogenesis also by improving the endothelial function. By reducing the AT II level, the oxidative stress is also reduced, decreasing nitric oxide activity. Thus, the balance between two vasoactive systems - AT II and NO is restored.

REFERENCES

1. Tase A. Cercetări comparative asupra eficienței terapeutice a unor inhibitori ai enzimei de conversie a angiotensinei, Editura Universității Pitești; 2007.
2. Pitt B, Jamerson KA, Vaughan DE. In Pursuit of BP Controland Improved End-Organ Protection: Optimizing RAS Suppression with Renin Inhibition. JACC. 2005;45-3 (Suppl. A):99A.
3. Gherasim L, Dorobantu M. Tratamentul hipertensiunii arteriale - principii și practică. Editura InfoMedica; 2004. p. 80.
4. Gottlieb SS, Dickstein K, Fleck E, Kostis J, Levine TB, Lejemtel T. Hemodynamic and neurohormonal effects of the angiotensin II antagonist losartan in patients with congestive heart failure, Circulation. 1993;88:1602-9.
5. Iyer SN, Ferrario CM, Chappell MC. Angiotensin (1-7) contributes to the antihypertensive effects of blockade of the renin-angiotensin system, Hypertension. 1998;31:356-61.
6. Ishiyama Y, Gallagher PE, Averill DB, Tallant EA, Brosnihan KB, Ferrario CM. Upregulation of angiotensin-converting enzyme 2 after myocardial infarction by blockade of angiotensin II receptors. Hypertension. 2004;43:970–6.
7. Tica A, Voicu V. Farmacologie, Editura Medicală Universitară Craiova; 2008.
8. Opie H, Gersh BJ. Drugs for heart, WB Saunders, Philadelphia; 2001.
9. Moser M, Izzo J, Sica D. The Use of Renin Inhibitors in the Management of Hypertension, The Journal of Clinical Hypertension. 2007;9(9).
10. Petkow-Dimitrow P. New therapeutic targets for ACE inhibitors and angiotensin receptor blockers, Pol Arch Med Wewn. 2007;117(4):44-50.
11. Martinez FA. Aldosterone inhibition and cardiovascular protection: more important than it once appeared, Cardiovasc Drugs Ther. 2010;24(4):345-50.

12. Keidar S, Gamliel-Lazarovich A, Kaplan M, Pavlotzky E, Hamoud S, Hayek T, et al. Mineralocorticoid receptor blocker increases angiotensin-converting enzyme 2 activity in congestive heart failure patients. Circ Res. 2005;97:946–53.
13. Pitt B, Zannad F, Remme WJ, Cody R, Castaigne A, Perez A, et al. for the Randomized Aldactone Evaluation Study Investigators. The effect of spironolactone on morbidity and mortality in patients with severe heart failure. N Engl J Med. 1999;341:709-717.
14. Leonetti G, Cuspidi C. Choosing the right ACE inhibitor. A guide to selection. Drugs. 1995;49:516-531.
15. Jackson EK. Renin and angiotensin in: Hardman JG, Limbird LE, Editors. The pharmacological basis of therapeutics. 10th Ed. New York; 2001. p. 809-841.
16. Tase A. Cercetari comparative asupra eficientei terapeutice a unor inhibitori ai enzimei de conversie a angiotensinei, Editura Universitatii Pitesti; 2007.
17. Hornig B, Kohler C, Drexler H. Role of bradykinin in mediating vascular effects of angiotensin converting enzyme inhibitors in humans. Circulation. 1997;95:1115-1118.
18. Tica A, Voicu V. Farmacologie, Colectia Hipocrate, Aius; 2004. p. 195.
19. Brunner F, Kukovetz WR. Postischaemic antiarrhythmic effects of angiotensin converting enzyme inhibitors. Circulation. 1996;94:1752-1761.
20. Mancini GBJ, Henry GC, Macaya C. Angiotensin converting enzyme inhibition with quinapril improve endothelial vasomotor dysfuncţion in patients with coronary artery disease. Circulation. 1996;94:258-265.
21. London GM, Pannier B, Vicaut E. Antihypertensive effects and arterial haemodynamic alterations during angiotensin converting enzyme inhibition. J Hypertens. 1996;14:1139-1146.
22. Schmieder RE, Martus P, Klingbeil A. Reversal of left ventricular hyperthrophy in essential hypertension. A meta-analysis of randomized double-blind studies. JAMA. 1996;275:1507-1513.
23. Gradman AH, Cutler NR, Davis PJ. Combined enalapril and felodipine extended release (ER) for systemic hypertension. Am J Cardiol. 1997;79:431-435.
24. Motz W, Strauer BE. Improvement of coronary flow reserve after long-term therapy with enalapril. Hypertension. 1996;27:1031-1038.
25. Anthony I, Lerebours G, Nitenberg A. Angiotensin converting enzyme inhibition restores flow-dependent and cold pressor test-induced dilations in coronary arteries of hypertensive patients. Circulation. 1996;94:3114-3122.
26. Yusuf S, Pepine CJ, Garces C et al. Effect of enalapril on myocardial infarction and unstableangina inpatients with low ejection fraction. Lancet. 1993;340:1173–8.
27. Teo KK, Yusuf S, Pfeffer M et al. for the ACE Inhibitors Collaborative Group. Effects of long-term treatment with angiotensin-converting enzymeinhibitors in the presence o rabsence of aspirin: asystematic review. Lancet. 2002;360:1037–43.
28. Cleland JGF, Erhardt L, Murray G. Effect of ramipril on morbidity and mode of death among survivors of acute myocardial infarction with clinical evidence of heart failure. Eur Heart J. 1997;18:41-51.
29. Badea G, Apetrei E. Hipertensiunea arteriala si stenoza aortica degenerativa – relatie de cauzalitate, consecinţe hemodinamice si perspective terapeutice, Revista Romana de Cardiologie. 2006;21(2):110-114.
30. McDonald KM, D'Aloia A, Parrish T. Functional impact of an increase in ventricular mass after myocardial damage and its attenuation by converting enzyme inhibition. Circulation. 1996;91:2043-2048.
31. Greenberg B, Quinones MA, Koilpillai C for the SOLVD Investigators. Effects of long-term enalapril therapy on cardiac structure and function in patients with left ventricular dysfunction. Circulation. 1995;91:2573-2581.
32. The SOLVD Investigators. Effects of enalapril on survival in patients with reduced left ventricular ejection fractions and congestive heart failure. N Engl J Med. 1991;325:293-302.
33. Sckoelkens BA, Landgraf W. ACE inhibition and atherosclerosis. Can J Physiol Pharmacol. 2002;80:354-9.
34. Lopez-Sendon J et al. Expert consensus document on angiotensin converting enzyme inhibitors in cardiovascular disease, European Heart Journal. 2004;25:1454-1470.
35. Lonn EM, Yusuf S, Dzavik V et al. Effects of ramipril and vitamin E on atherosclerosis: the study to evaluate carotid ultrasound changes in patients treated with ramipril and vitamin E (SECURE). Circulation. 2001;103:919–25.
36. Swedberg K. Importance of neuroendocrine activation in chronic heart failure. Impact on treatment strategies. Eur J Heart Fail. 2000;2:229–33.
37. Ubaid-Girioli S, Leoní A, Yugar-Toledo JC, Martins LC. Aldosterone Excess or Escape: Treating Resistant Hypertension, Journal of Clinical Hypertension. 2009;11 (5):245-252.
38. Filimon S. Riscul trombotic: noţiuni generale şi particularităţile lui la bolnavii cu hipertensiune arterială, Arta Medica. 2006;1(16):43-48.
39. Brown NJ, Vaughan DE. Prothrombotic effects of angiotensin, Adv Interrn Med. 2000;45:419-429.