



Kasuistika | Case report

The importance of a higher dose of a mineralocorticoid receptor antagonist in reducing risk of recurrent hospitalization in a patient with advanced chronic heart failure – A case report

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SOUHRN

Autoři upozorňují na význam podávání vyšší dávky antagonisty mineralokortikoidních receptorů pro snížení frekvence hospitalizací 67letého pacienta s pokročilým chronickým srdečním selháním.

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ABSTRACT

The authors present the significance of a higher dose of a mineralocorticoid receptor antagonist in reducing the frequency of hospitalizations for decompensated heart failure in the 67-year-old patient suffering from advanced chronic heart failure.

Introduction

Heart failure is defined as a state when the heart is unable to pump blood with normal venous return according to the needs of tissue metabolism or a state when it is only able to do so with an increased ventricular filling pressure. The human body deals with a heart function disorder through adaptation mechanisms that are harmful if they are active over the long-term, mainly concerns the activation of the sympathetic nervous system and the renin–angiotensin–aldosterone system (RAAS). The short-term effects include increased heart activity, vasoconstriction and fluid retention, and the long-term effects are myocyte hypertrophy, apoptosis and myocard fibrosis (left ventricular remodeling). There is also an increase in the production of vasodilatation mediators (prostaglandins, natriuretic peptides, bradykinin and others); however, these are unable to compensate for the adverse effects of vasoconstriction mediators. Diuretics are well-established in treatment, as are positive inotropic agents administered in the short-term for acute or decompensated chronic heart failure. However, the highest success rate has been achieved through the administration of medication that affects the sympathetic nervous system and the RAAS.

Three groups of RAAS blocker are used in the clinical practice: inhibitors of the angiotensin-converting enzyme (ACE inhibitors), angiotensin II AT₁ receptor blockers (AT₁ blockers) and mineralocorticoid receptor blockers (MRA).

Neither ACE inhibitors, nor AT₁ blockers have a sufficient effect on the increased aldosterone production. The prolonged activity of aldosterone causes fibrosis in the heart, the development of cardiac remodeling and ventricular arrhythmias. Spironolactone is the basic medication in the group of mineralocorticoid receptor blockers. In some patients, its administration is limited due to adverse endocrine effects. These complications have been eliminated by eplerenone, a spironolactone derivative that has been verified in clinical studies in patients post-myocardial infarction left ventricular dysfunction as well as in patients with less advanced CHF. The verification of the positive effects of mineralocorticoid receptor blockers has been confirmed by several clinical studies – RALES with spironolactone, EPHEsus and EMPHASIS-HF with eplerenone [1–3] (Table 1).

In 1999, the RALES study proved a decrease in the mortality with a reduction in the hospitalization rate for patients with NYHA III and IV heart failure treated with spironolactone compared to placebo. The EPHEsus study published in 2003 contributed to the expanded indication of aldosterone antagonists; adding eplerenone to the established medication for left ventricular dysfunction in post-myocardial infarction patients resulted in a decrease in both the mortality and the frequency of hospitalizations. The EMPHASIS-HF clinical study published in 2011 shifted the use of eplerenone towards patients with chronic heart failure and left ventricular systolic dysfunction with mild symptoms (NYHA II).

Eplerenone was developed in the effort to eliminate the adverse effects of the secondary hormonal effects of spironolactone. Chemically, it is 9 α ,11-epoxy-mexrenone (CGP 30383) with the generic name eplerenone. In ex-

Table 1 – Clinical trials of MRAs in heart failure.

Acronym	Year of publication	Design	Number of patients	Average age	Characteristics	Follow-up (median)	End-point	Result	p
RALES	1999	Spironolacton vs. placebo ^a	1663	71	NYHA III–IV LVEF \leq 35%	24 M	CV mortality Mortality	–30.00% –31%	<0.001 <0.001
EPHEsus	2003	Eplerenone vs. placebo	6632	64	Post-MI HF LVEF 33%	16 M	Hospitalization for HF CV mortality/CV hospitalization Mortality	–35% –13% –13%	<0.001 0.002 0.008
EMPHASIS-HF	2011	Eplerenone vs. placebo	2737	69	NYHA II LVEF \leq 35%	21 M	CV mortality CV mortality/hospitalization for HF Mortality	–17% –37% –24%	0.005 0.001 0.008

^a Placebo – standard treatment including ACEI, potentially beta-blockers; CV – cardiovascular; HF – heart failure; MI – myocardial infarction; MRA – mineral corticoid receptor antagonists.

periments conducted on animals and healthy volunteers, the effectiveness of the doses 25 mg, 50 mg and 75 mg was proved, the dependence of natrium excretion on the dose was confirmed and the equipotence of the 50 mg dose of eplerenone with 50 mg of commercial spironolactone was determined. It was patented in 1985 and put on the market in the form of 25 mg and 50 mg coated tablets, and it was indicated so far exclusively as a supplement to standard therapy (including beta-blockers) for post-myocardial infarction left ventricular dysfunction when the ejection fraction falls below 40% and clinical symptoms of heart failure.

In clinical trials, its use resulted in a decrease in both the mortality and the frequency of hospitalizations; however, unlike spironolactone, the occurrence of hormonally mediated disorders such as gynecomastia and erectile dysfunction is nearly twenty times lower after the administration of eplerenone. The paracrine blockade of aldosterone, in particular the reduction in collagen production and perivascular fibrosis, is interpreted as a beneficial effect of long-term eplerenone administration. The bioavailability of eplerenone exceeds 90%, and the excretion half-time is 3.5–5 hours; just as spironolactone, it is metabolised by cytochrome P450 in the liver, and two thirds are excreted in urine. Eplerenone has a lower affinity for mineralocorticoid receptors compared to spironolactone, but its affinity for androgen and progesterone receptors is lower by orders of magnitude. The occurrence of gynecomastia was much lower in the EPHEsus study compared to the RALES study (0.5%/0.6% compared to 9%/1%), and it was basically at the level of a placebo. As for natrium excretion and impact on the Na/K quotient, the effect of both medications is the same; it is easier to regulate in eplerenone – thanks to pharmacokinetics. The occurrence of hyperkalemia with eplerenone administration was significantly higher than with the placebo administration; the statistical difference in the occurrence of other adverse effects was insignificant.

The reason for use of mineralocorticoid receptor antagonists is based on the fact that the long-term application of ACE inhibitors and AT1 blockers results in a higher concentration of aldosterone, which is undesirable according to all the indications. Therefore, any treatment based on MRA becomes ineffective at a certain point.

When the dose is chosen correctly, MRAs also contribute to the correction of the potassium depletion known to be caused by the ingestion of loop diuretics used in CHF therapy. In terms of clinical pharmacology, eplerenone has obvious advantages in comparison with spironolactone.

Case report

A male patient, born in 1950, with chronic heart failure caused by coincidence of ischemic heart disease (IHD) and dilated cardiomyopathy (DCM). In 1999, he was diagnosed with IHD after a transmural infarction of the inferior wall that was solved with a PTCA. He had already been diagnosed with heart failure at that point; the echocardiogram confirmed a systolic function depression in a dilated left ventricle with a 30–35% ejection fraction. Repeated

selective coronary angiography and angioplasty of LAD took place in 2003. In 2007, the patient was indicated for heart resynchronization therapy and an ICD implantation in primary prevention of sudden cardiac death.

The patient had many comorbidities – chronic atrial fibrillation, type 2 diabetes mellitus, chronic renal insufficiency, chronic obstructive pulmonary disease, metabolic syndrome and hypothyreosis. Patient was contraindicated for heart transplantation because of the comorbidities.

In 2011, he was indicated for cardiac surgery due to significant ischemic mitral and functional tricuspid regurgitation. CABG (coronary artery bypass grafting), MVR (bioprosthetic mitral valve replacement), TVR (bioprosthetic tricuspid valve replacement) and Cryo MAZE were performed. For further treatment management and therapy titration, the patient was sent to a heart failure clinic. Here, titration of the set therapy was performed; nonetheless, the patient's condition required repeated hospital treatment for cardiac decompensation.

The patient did not tolerate the treatment with angiotensin converting enzyme inhibitors for symptomatic hypotension in concurrent therapy with BB and diuretics.

The recurrent signs of cardiac decompensation and hypervolemia have been established in the course of further patient monitoring. Diuretic treatment was increased in the therapy, spironolactone was replaced with eplerenone (intolerance of spironolactone – gynecomastia – had been documented for the patient) and the eplerenone dose was up-titrated. The patient was repeatedly reeducated on the necessity to follow diet and regimen measures (fluid and salt restrictions). After setting the therapy, clinical stabilization was achieved, and the patient's condition improved. Progression of his condition with heart failure decompensation occurred, and the need for hospitalization arose in March 2015; diuretic therapy was intensified. The dose of eplerenone was increased to 200 mg/day with frequent renal function controls. The condition stabilized after that, enabling discharge. The patient was followed on regular basis in a tertiary care clinic; chronic heart failure medication included carvedilol 12.5 mg 1-0-1, eplerenone 50 mg 2-0-2, furosemide 250 mg 1-1-0, hydrochlorothiazid 25mg 1-0-0). His status remained stable until March 2016, requiring i.v. diuretic treatment in the hospital. He was discharged clinically stable, functionally at NYHA II. From March 2016 to January 2017 the patient's status did not require repeated hospitalization.

Unfortunately, the patient was admitted again to the hospital in January 2017 and in March 2017 the heart failure progressed to refractory stage and the patient died in the hospital of multiorgan failure as a consequence of advanced heart failure.

Conclusion

The clinical studies followed by the clinical practice have shown an improvement in morbidity, mortality and a reduction in the number of hospitalizations for heart failure after eplerenone was added to the standard treatment of patients with chronic heart failure and left ventricular systolic dysfunction. For safe treatment with eplerenone,

Table 2 – Diuretic dose in chronic heart failure (modified from [5])

	Loading dose		Target dose	
Loop diuretic				
Furosemide	20–40		40–240 (250 mg)	
Thiazid diuretic				
Hydrochlorothiazide	25		12.5–100	
Indapamid	2.5		2.5–5	
Potassium sparing diuretic	Regular and (–ACEI/ARB)		Regular and (–ACEI/ARB)	
Spironolactone/eplerenone	12.5–25	50	50	100–200
Amiloride	2.5	5	5–10	10–20

(–ACEI/ARB) – diuretic dose in absence of ACEI or AT₁ blocker (intolerance or contraindication)

an optimum dosage with regard to the current potassium level, renal function and careful laboratory monitoring is essential. According to the ESC practice guidelines for acute and chronic heart failure diagnostics and treatment, the administration of MRA (spironolactone and eplerenone) is recommended to all symptomatic patients (regardless of ACEI and beta-blocker treatment) with HFrEF and LVEF at $\leq 35\%$ with the aim to decrease mortality and hospitalization for heart failure. Caution must be taken in cases when MRA is administered to patients with impaired renal function and patients with serum potassium concentrations at > 5.0 mmol/l.

High initial and maintenance doses of MRA are necessary in patients with contraindications or patients who do not tolerate ACEI or ARB treatment [4,5] (Table 2).

Our case report demonstrates that use of higher dose of MRA in addition to other drug therapy might be useful in patients with advanced heart failure without other treatment options. High doses of eplerenone were associated with reduction of the frequency of hospital admissions and need of i.v. diuretic treatment. This approach probably also delayed the inevitable fatal course of the disease.

Conflict of interest

None declared.

Funding body

None.

Ethical statement

Authors state that the research was conducted according to ethical standards.

Informed consent

The authors declare that informed consent was obtained from the patient participating in this study.

References

- [1] B. Pitt, F. Zannad, W.J. Remme, et al., The effect of spironolactone on morbidity and mortality in patients with severe heart failure, *New England Journal of Medicine* 341 (1999) 709–717.
- [2] B. Pitt, W. Remme, F. Zannad, et al., for the Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study Investigators, Eplerenone, a selective aldosterone blocker, in patients with left ventricular dysfunction after myocardial infarction, *New England Journal of Medicine* 348 (2003) 1309–1321.
- [3] F. Zannad, J.J.V. McMurray, H. Krum, et al., Eplerenone in patients with systolic heart failure and mild symptoms, *New England Journal of Medicine* 364 (2011) 11–21.
- [4] P. Ponikowski, A.A. Voors, S.D. Anker, et al., ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC), *European Heart Journal* 18 (2016) 891–975.
- [5] J. Špinar, J. Hradec, L. Špinarova, J. Vitovec, Souhrn Doporučených postupů ESC pro diagnostiku a léčbu akutního a chronického srdečního selhání z roku 2016, *Cor et Vasa* 58 (2016) e530–e568.