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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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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 a 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 be 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 administred in the short-term for acute or decompensated chronic heart failure.

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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 toward 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 9α,11-epoxy-mexrenone (CGP 30383) with the generic name eplerenone. In experiments 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 h; just as spironolactone, it is metabolized 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 MRAs becomes ineffective at a certain point.

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	Spironolactone vs. placebo[a]	1663	71	NYHA III–IV	24 M	CV mortality	−30.00%	<0.001
					LVEF ≤35%		Mortality	−31%	<0.001
							Hospitalization for HF	−35%	<0.001
EPHESUS	2003	Eplerenone vs. placebo	6632	64	Post-MI HF	16 M	CV mortality/CV hospitalization	−13%	0.002
					LVEF 33%		Mortality	−13%	0.008
							CV mortality	−17%	0.005
EMPHASIS-HF	2011	Eplerenone vs. placebo	2737	69	NYHA II	21 M	CV mortality/ hospitalization for HF	−37%	0.001
					LVEF ≤35%		Mortality	−24%	0.008

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

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