VIA MEDICA

CASE REPORT

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Eplerenone add-on treatment in resistant hypertension in a peritoneal dialysis patient. A case report

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ABSTRACT

Resistant hypertension (RH) is frequently seen in clinical practice in kidney disease patients. Mineralocorticoid receptor antagonists (MRAs) especially spironolactone are highly effective in the management of RH. Eplerenone — highly selective MRA has been also shown to be effective in RH patients but it is rarely used in this clinical condition, especially in kidney disease patients. Eplerenone is mainly recommended in congestive heart failure after myocardial infarction. A case of peritoneal dialysis (PD) patient with RH successfully treated with eplerenone was reported.

Key words: peritoneal dialysis, resistant hypertension, mineralocorticoid receptor antagonists, eplerenone

Introduction

Hypertension is a common clinical problem in the dialysis population. It affects approximately 60–80% of hemodialysis (HD) patients and 30% to 90% of peritoneal dialysis (PD) patients [1]. Hypertension is prevalent and usually poorly controlled. Fluid overload and sodium retention are the main pathogenic factors in the dialysis population. The other factors are increased renin-angiotensin-aldosterone system (RAAS) activity, increased arterial stiffness, overactivation of the sympathetic nervous system, peritoneal membrane characteristics, erythropoiesis-stimulating agents (ESAs) administration or sleep apnoea syndrome [1]. In PD patients residual kidney function loss and deterioration of peritoneal membrane function are considered to be essential factors of deterioration of blood pressure control [2, 3]. Resistant hypertension (RH) is defined as the inability to achieve goal blood pressure despite the use of 3 or more appropriately dosed antihypertensive drugs including a diuretic. It affects 10–20% of hypertensive patients. RH is an important clinical problem in hypertensive chronic kidney disease (CKD) patients both on conservative and renal replacement therapy (RRT) treatment. The consequences of RH are the risk of progression of CKD to the end-stage phase, accelerated organ damage and increased cardiovascular risk [4, 5].

This study describes a case of a 37-year–old man with diabetic kidney disease and end-stage kidney disease (ESKD) with resistant hypertension on PD who was successfully treated with eplerenone added-on standard antihypertensive therapy.

Case report

A 37-year-old Caucasian man with type 1 diabetes mellitus was diagnosed in childhood (at the age of 14 years old), with diabetic kidney disease and ESKD. He was also suffering from long-lasting hypertension, proliferative retinopathy, reflux esophagitis and chronic gastritis. Moreover, his important medical problems were renal anemia and chronic kidney disease — mineral and bone disorder (CKD-MBD). He started continuous ambulatory peritoneal dialysis (CAPD) treatment on 10th August 2019, 3 weeks after peritoneal catheter insertion. His treatment regimen was: 4 exchanges of

PD-4 1,36% Physioneal fluid (Baxter, USA) with an inflow volume of 2,0 litres. After 2 months the patient was transferred from CAPD to automated peritoneal dialysis (APD) using the Home Choice Claria cycler. This time his dialysis prescription was: 12,0 litres of PD-4 1,36% Physioneal fluid. He reached daily ultrafiltration of approximately 700–850 ml and his residual diuresis was approximately 1,5 litre daily. In June 2021 he started all necessary procedures for qualification for both pancreas and kidney transplantation. In August 2021 because of high blood pressure, his PD fluids were changed and a new PD regimen was prescribed: PD-4 1,36% Physionel 5000 mL and 2,27% Physioneal 5000 ml. He achieved a higher ultrafiltration volume of approximately 1000–1200 mL. After 4 weeks on the routine visit, his vital signs were as follows: the temperature was 36,6°C, heart rate was 100 beats per minute, no additional murmurs were heard, respiration rate was 16 per minute and no signs of lung congestion. His blood pressure was 160/96 mmHg. No peripheral oedema was present. Laboratory tests were presented in Table 1.

Antihypertensive medication was as follows: amlodipine 2 × 10 mg b.i.d., furosemide 120 mg daily, nebivolol 5 mg once a day, perindopril 10 mg once a day, doxazosin 2 × 2 mg b.i.d. He was also prescribed: atorvastatin 20 mg, oral iron — tardyferon 80 mg (ferrosi sulfas) and folic acid 5 mg daily. Renal anemia was treated with darbepoetin alfa s.c., (dose was 20 mcg monthly) and CKD-MBD was treated according to the 2017 KDIGO CKD-MBD Guideline Update (calcium carbonate in a dose 3 × 3.0 g daily, alfadiol 0.25 mcg per day). There were no signs of infectious complications of PD during the last 3 months. The patient was also given a non-pharmacological recommendation for hypertension treatment — dietary salt restriction (< 5.0 g/day). He was also given a low-potassium and phosphorus diet. Because of unsatisfactory results of home blood pressure monitoring (HBPM), (mean values from the last 7 days were 150/95 mmHg) it was decided to increase the doxazosin dose to 2 × 4 mg daily. Moreover, the PD fluids regimen was changed and icodextrin (Extraneal, Baxter) 1500 mL was added as a last bag. After 4 weeks of treatment, an unsatisfactory blood pressure control (HBPM-mean values: 145/95 mmHg) was reported. Therefore, we have decided to initiate MRA treatment. Eplerenone was prescribed at a daily dose of 50 mg (2 × 25 mg daily). In the meantime, according to Doppler ultrasound examination renal artery stenosis was excluded. Before initiating eplerenone treatment, ambulatory blood pressure monitoring (ABPM) was performed. His mean daily blood pressure was: 159.1/99 mmHg, mean blood pressure during daily activities was 158.9/96,8 mmHg and mean nighttime blood pressure was 160/110 mmHg. ABPM showed a reverse-dipper blood pressure profile. The patient was also given a prescription for a low-potassium diet.

Table 1. Laboratory parameters at routine visit at PD outpatient

Parameter	Value	Reference value
WBC [$10^3/\mu$L]	6.5	3.98–10.04
RBC [$10^6/\mu$L]	3.12	3.93–5.22
HGB [g/dL]	10.9	11.2–15.7
HCT [%]	30.3	34,1–44,9
MCV [fl]	87.5	79.4–94.6
MCH [pg]	29.3	25.6–32
MCHC [g/dL]	33.5	32.2–35.3
PLT [$10^3/\mu$L]	344	132–370
CRP [mg/L]	0.5	< 5.00
BUN [mg/dL]	65	9.0–23.0
Glucose level [mg/dL]	127	70–99
Potassium [mmol/L]	4.2	3.5–5.5
Sodium [mmol/L]	141.2	136.0–145.0
Chloride [mmol/L]	105.1	98.0–107.0
Serum creatinine [mg/dL]	5.25	0.50–0.80
eGFR [mL/min] CKD-EPI	14	> 60.0
Procalcitonin [ng/mL]	0.07	< 0.50
Total cholesterol [mg/dL]	220	< 190
Albumin [mg/dL]	3.8	3.4–4.8
Total protein [mg/dL]	6.58	6.0–7.8
Serum calcium [mmo/L]	2.43	2.20–2.50
Phosphorus [mmo/L]	1.76	0.74–1.52
PTH [pg/mL]	764	15.0–68.3

After 6 weeks of treatment, an improvement in blood pressure control was reported. According to HBPM there was acceptable blood pressure control and mean values from the last 7 days were 133/78 mmHg. His blood pressure in the office was 135/80 mmHg. Hyperkalaemia episodes were not observed after the commencement of MRA treatment. The potassium level on the routine visit was 4.9 mmol/L. Unfortunately, there was no time for another ABPM evaluation, because, in the meantime, the patient received simultaneous pancreas-kidney transplantation (SPKT) (12 November 2021).

Discussion

Mineralocorticoid receptor antagonists (MRAs) are a valuable therapeutical option in hypertension, congestive heart failure (CHF) and chronic kidney disease (CKD). They are also recommended for resistant hypertension (RH). Excess of aldosterone plays a crucial role in the pathogenesis of RH. Aldosterone is produced in

the adrenal cortex and fat tissue. It is responsible for sodium and potassium balance via the activation of the mineralocorticoid receptor in distal tubules and collecting ducts of the kidneys. Aldosterone production is stimulated by angiotensin II, increased serum potassium level and corticotropin activity. Aldosterone overproduction induces salt and water retention, thus resulting in elevated blood pressure. Moreover, deleterious effects of aldosterone excess include increased sympathetic system activity, endothelial dysfunction, oxidative stress and increased expression of genes involved in inflammation, fibrosis and calcification. Due to higher intravascular volume in patients with RH, especially in kidney diseases, the use of diuretics is mandatory. MRAs seem to be an essential part of such treatment [6, 7].

In CKD patients on conservative treatment, MRAs are rarely used because of the risk of hyperkalaemia and according to the current guidelines, treatment with its use should not be initiated in CKD patients with eGFR < 30 mL/min or serum potassium level > 5.0 mmol/L. In a few studies in predialysis CKD patients, MRAs had been shown to reduce proteinuria and improve cardiovascular system function [8]. Cardioprotective effects of MRAs had been also shown in many reports in HD patients, but their influence on mortality is still a matter of debate [6]. Compared to HD patients, there were only a few reports of successful treatment with MRAs in PD patients with congestive heart failure (CHF). Hausmman described an improvement in cardiac function expressed as an increase in ejection fraction (from 32% to 46%) in PD patients treated with spironolactone at a daily dose of 25mg for 10 months [9]. Reduction of a left ventricular mass index (LVMI) in 146 PD patients on ACE-I or ARB and spironolactone added to this treatment was reported by Ito et al. [10]. An important indication to start MRAs treatment in PD patients is also hypokalaemia persistent despite oral potassium supplementation [11, 12]. Moreover, attenuation of processes of degradation of the peritoneal membrane during long–term PD treatment was reported in patients on MRAs administration [13, 14].

RH is another clinical condition to start mineralocorticoid antagonist treatment. RH is highly prevalent in the CKD population. According to observational studies, the prevalence of RH is ranging from 2 to 30% of treated hypertensive patients [15]. The consequences of RH are more pronounced target organ damage i.e. left ventricular hypertrophy (LVH), carotid plaque formation, and increased arterial stiffness. Because of the overactivation of the renin–angiotensin–aldosterone system (RAAS) in kidney diseases ACE-Is and ARBs are often prescribed in both predialysis CKD and dialyzed patients. Thus, these two agents can not eliminate the "aldosterone escape phenomenon" defined as an inability to suppress aldosterone release, which can be observed in 30–50% of patients on ACE-Is/ARBs treatment. High aldosterone levels may be observed not only in CKD patients but in obesity or obstructive sleep apnea (OSA) also. The crucial role of spironolactone treatment in RH patients was established in the PATHWAY-2 study. In this randomized, double-blind, cross-over trial spironolactone was more effective than doxazosin or bisoprolol as an add-on drug for the treatment of really resistant hypertension [16].

The beneficial effects of MRAs added to antihypertensive treatment were reported in CKD patients on conservative treatment and in several studies conducted in HD patients. In the HD population spironolactone was used in a daily dose range from 25 mg to 100 mg and a beneficial effect was reported despite changes in residual renal function [17–19]. In most clinical trials in CKD and RH patients (both in predialysis, HD and PD individuals) classical non-selective spironolactone in one daily dose was used.

Eplerenone a selective mineralocorticoid receptor antagonist is an effective alternative to spironolactone. Eplerenone is especially indicated in patients with left ventricular ejection fraction (EF) ≤ 40% and clinical symptoms of heart failure secondary to myocardial infarction. In two crucial clinical trials in patients with reduced EF (EPHESUS Study and EPHASIS- HF), eplerenone led to a reduction in cardiovascular mortality [20]. Eplerenone was revealed to be effective in RH patients. However, in contrast to spironolactone studies for RH, studies with eplerenone use in RH are scarce. In several case reports and small studies eplerenone was prescribed in RH patients. Eguchi K. et al reported lowering in-home and ambulatory BP monitoring in 35 RH patients on eplerenone added-on treatment (eplerenone was prescribed once daily in a dose of 25 mg or 50 mg for 12 weeks) in comparison to control. Moreover, the authors reported some changes in measurements of target organ damage, they indicated an increase in flow-mediated vasodilatation (FMD) measurements after 12 weeks of treatment but no changes in urinary albumin/creatinine ratio and pulse wave velocity (PWV) between eplerenone group and control. In this study patients with hyperkalaemia (K > 5,0mmo/L) and renal dysfunction (eGFR < 50 mL/min) were excluded [21]. The beneficial effect of eplerenone treatment was also confirmed by Weinberger et al. (reduction in SBP and DBP in eplerenone group vs placebo group) and by Flack et al. (eplerenone was more effective than losartan in low renin group) [20]. In comparison to spironolactone, eplerenone has a shorter half-life and it should be prescribed twice a day. Moreover, eplerenone is more selective, without anti-androgenic effects like gynecomastia, hirsutism or sexual dysfunction [22, 23].

Treatment of hypertension in the population of PD patients requires the achievement of individual "dry

weight" by sodium and water restriction, adjunctive use of loop diuretics in presence of residual renal function, an adaptation of PD regimen to peritoneal membrane characteristics and combined anti-hypertensive therapy in most cases. In the authors' opinion, in the presented patient, all these methods were applied. Besides combined antihypertensive pharmacologic therapy and icodextrin treatment, add-on therapy with eplerenone was associated with improvement in blood pressure control. This therapy was well tolerated and safe without hyperkalaemia episodes during treatment.

Conclusions

Add-on therapy with eplerenone is a valuable option for RH treatment in PD patients. Eplerenone should be considered as an alternative to spironolactone and preferred in therapy because of good tolerance and lack of anti-androgenic side effects. Larger clinical trials evaluating the role of eplerenone treatment in RH in PD patients are required.

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