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Intravenous mineralocorticoid receptor antagonist use in acutely decompensated heart failure with diuretic resistance

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Pharma, Idorsia, NovoNordisk, Ablative Solutions, G3P, Corvidia, Relypsa, and is the cofounder of CardioRenal, a company developing a telemonitoring loop in heart failure (including potassium measurements). Pr Girerd reports personal fees from Novartis and Boehringer. Other coauthors have no disclosures.

Abstract

Intravenous mineralocorticoid receptor antagonists MRAs have been used in some centers for decades to reduce the risk of hypokalemia and boost diuresis in acutely decompensated heart failure (ADHF). We report the well-tolerated use of Intravenous MRAs as a rescue procedure in 3 patients admitted for ADHF with important diuretic resistance. Undertaking trials evaluating the effect of this therapeutic strategy in ADHF could represent a promising avenue.

Key words:

Heart failure; Mineralocorticoid Receptor Antagonist; Dyspnea; Cardiac Edema; Cardiovascular diseases; Potassium Canrenoate.

The implementation of renin-angiotensin blockers in the past 30 years has had a profound impact on the rates of hospitalization and death of ambulatory patients with heart failure and reduced ejection fraction (HFrEF). Nevertheless, in-hospital mortality after an episode of acutely decompensated HF (ADHF) still hovers at almost 10% and the readmission risk soon after discharge remains unacceptably high.

While guidelines recommend the use of mineralocorticoid receptor antagonists (MRA) in ambulatory patients, their use in ADHF is not specifically stipulated. We previously reported evidence of the benefit of MRA initiation within 6 weeks following discharge from ADHF.¹ In addition, we also reported that patients admitted for ADHF have elevated serum aldosterone levels which, in turn, are associated with worse clinical outcome following discharge.² Renin angiotensin system blockers furthermore exhibit decongestion properties,³ and favorable MRA effects are accompanied by increased natriuresis and hemoconcentration, which are very likely related to decongestion. There is consequently a strong rationale for MRA use in the setting of ADHF. Recently, the ATHENA-HF trial reported a neutral association of spironolactone use with changes in NtProBNP.⁴ However, spironolactone is a pro-drug⁵ with a long metabolic life and therefore necessitates a long time to become active. Intravenous (IV) forms of MRAs could hence have a more rapid and thus potent effect in the setting of ADHF.

Several centers (e.g. Lyon Croix-Rousse University Hospital, France) have been using IV MRAs (potassium canrenoate) for decades to reduce the risk of hypokalemia and boost diuresis in patients with ADHF. Surprisingly, this approach has been reported more than 40 years ago, but has been long forgotten in most centers.^{6,7} Of note, the use of IV MRAs is not mentioned in current HF guidelines, which strongly suggests that their use are at best marginal worldwide. We consequently report herein the use of IV MRAs in the setting of diuretic resistance in 3 patients admitted for ADHF.

Case presentations

First case: 84-year-old man with HFrEF due to ischemic and valvular heart disease, admitted for ADHF. Initiation of MRA was considered when urine output remained low despite administration of high doses of loop diuretics and thiazide. Intravenous MRA was prescribed at 100 mg while furosemide was increased to

500 mg/day and hydrochlorothiazide to 25 mg/day, with diuresis at 400 mL over the prior 24 hours. Within the next 24h, urine output increased from 400 mL/day to 2800 mL/day. Creatinine dropped from 30.5 mg/L to 25.7 mg/L. Potassium remained stable and below 4.5 mmol/l. The patient lost 11 kg over the next 5 days (Figure 1, panel A).

Second case: 66-year-old man with hypertension, diabetes, chronic kidney disease and HFrEF due to ischemic heart disease, admitted for ADHF. The initial diuretic treatment was 20 mg/day IV bumetanide and 25 mg/day hydrochlorothiazide. Despite this maximal diuretic treatment, diuresis was only 1 l/day. A 100 mg/day dose of IV MRA was administered during 6 days while maintaining the remaining diuretic treatment unchanged. Urine output increased to 1.3 l on the first day of MRA treatment, subsequently increasing to 4.6 l/day on day 4. Concurrently with decongestion, serum creatinine decreased from 25.6 to 16.4 mg/L. Serum potassium remained below 4.5 mmol/L (Figure 1, panel B) and BP was unchanged after canrenoate initiation.

Third case: 85-year-old man with HFrEF due to ischemic HFrEF (LVEF 25%) and chronic kidney disease. This case being more complex than the first 2 cases, a detailed table is provided in Panel C. The patient was admitted after a weight increase of more than 10 kilos. Despite the use of continuous infusion of Bumetanide (25 mg/day) and 50 mg/day hydrochlorothiazide, diuresis remained less than 1.25 liters/day. Given that dialysis appeared extreme in an 85-year old advanced HF patient, Canrenoate (100 mg twice a day) was initiated as a last resort therapeutic option. In the next 3 days following Canrenoate initiation, diuresis increased to 1.50-1.80 liters/day. Soon after Canrenoate initiation, as the patient's condition started to improve, Valsartan 40 mg/day was introduced. This latter drug was very poorly tolerated with development of severe hypotension (systolic BP<90 mmHg with a BP drop > 40 mmHg) in the following days resulting in worsening renal function (maximum creatinine 35 mg/l) and oliguria. Given the patient's comorbidities, age and advanced HF status, conservative treatment in the cardiology ward was preferred to intensive care unit management. Seven days after Canrenoate initiation, while maintaining maximum diuretic treatment (Hydrochlorothiazide 50 mg/day and Bumetanide 25 mg/day) and resolution of the hypotension after Valsartan discontinuation, diuresis increased up to 5.0 liter/day. In the next days, the patient achieved his

normal dry weight (65 kilos) while renal function stabilized. Importantly, potassium remained <5 mmol/l during Canrenoate treatment.

Discussion

The aforementioned 3 cases illustrate the safety and possible efficacy of IV MRA use as a rescue procedure in treating patients admitted for ADHF with (sometimes extreme) diuretic resistance. In all three cases, creatinine noticeably improved while decongestion was achieved and serum potassium serum levels remained under 5 mmol/l. This appears rather reassuring in these patients at high-risk of worsening renal function. In case 3, while worsening renal function did occur, this occurrence was observed immediately following hypotension likely related to Valsartan introduction. Canrenoate was maintained despite worsening renal function and creatinine finally decreased when decongestion was ultimately achieved. In this case, we believe the delayed diuretic response to Canrenoate may well be the consequence of the hypotension episode. Importantly, the 3 cases suggest the excellent safety of Canrenoate with regard to blood pressure: indeed, Canrenoate initiation did not have any significant impact on BP in all 3 cases.

As emphasized repeatedly,⁸ the fear of worsening renal function should not prevent from targeting adequate decongestion in ADHF. In addition, in patients with maximal loop diuretic doses in the setting of diuretic resistance, hypokalemia (rather than hyperkalemia) is the real concern. MRAs can actually help prevent hypokalemia and the effect of MRA has been shown by our group to be more pronounced in patients with low serum potassium.⁹ In addition, these cases may even suggest a potential beneficial impact of IV MRAs on diuretic resistance. Urine output rose considerably after MRA initiation while the dosage of all other diuretics was maintained in case 2. In case 3, diuresis increased moderately soon after MRA initiation and further rose substantially 7 days after initiation, after resolution of low BP following Valsartan discontinuation.

The ATHENA-HF trial⁴ reported a neutral association of spironolactone use in patients admitted for ADHF. However, as stated earlier, spironolactone is a pro-drug and obtaining sufficient active blood concentrations of MRA could possibly take days. Such pharmacokinetic profile thus appears suboptimal in the setting of ADHF and other approaches should be envisaged, such as intravenous active forms of MRAs (e.g.

potassium canrenoate). We believe this active form is more likely to have an early impact on decongestion through increased natriuresis in patients admitted for ADHF.

Of note, the most appropriate dosage to be used in ADHF is still to be determine. In the first case, as a rapid and sizeable increase in diuresis was observed after the first 100 mg potassium canrenoate infusion, we stopped MRAs after this first infusion. In the second case, 100 mg potassium canrenoate per day was used for a longer period as the diuresis significantly rose only at 72 hours. In the last patient, a higher dose (100 mg twice a day) was used as all of the other diuretics were at maximum dosage; in this patient, we wanted to maximize the chance of diuresis response as canrenoate was truly perceived as the last rescue approach.

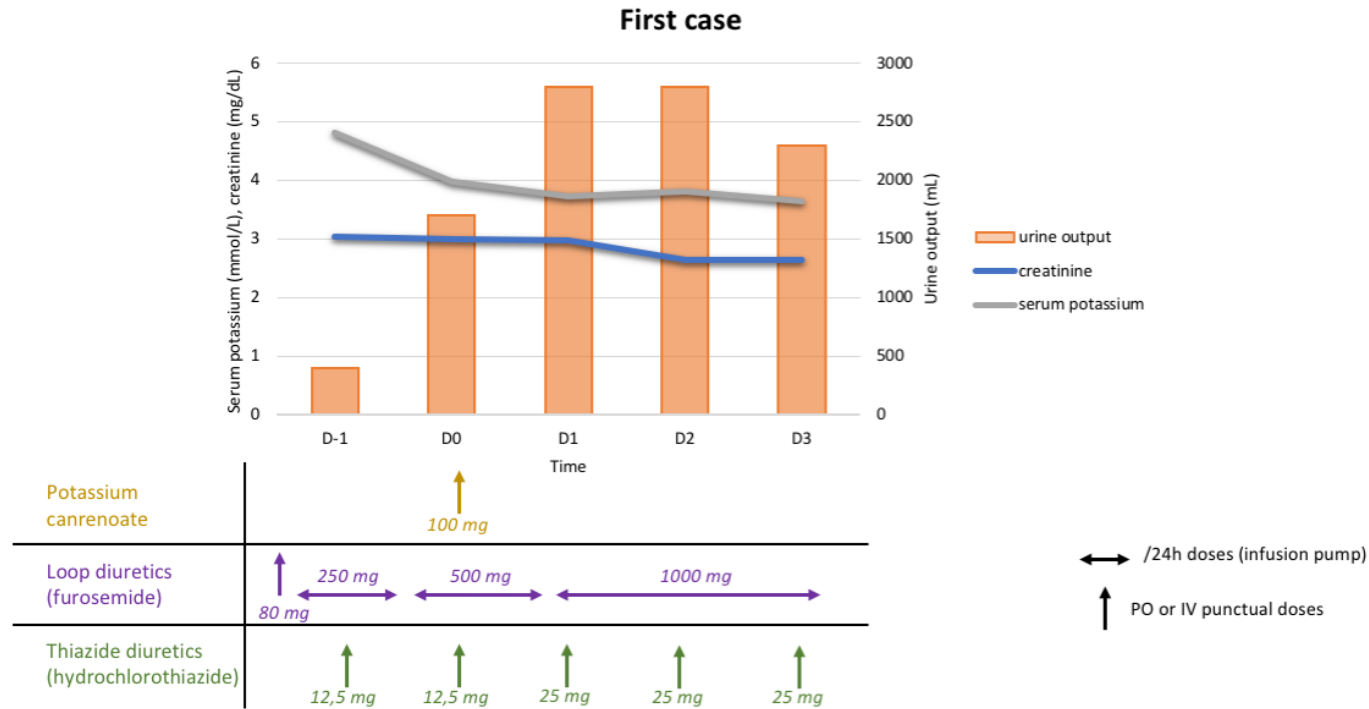
Take home message

We report herein that IV MRAs are well tolerated as a rescue therapy in very severe patients with diuretic resistance while being hospitalized for ADHF. Undertaking trials evaluating the effect of this therapeutic strategy in ADHF could represent a promising avenue.

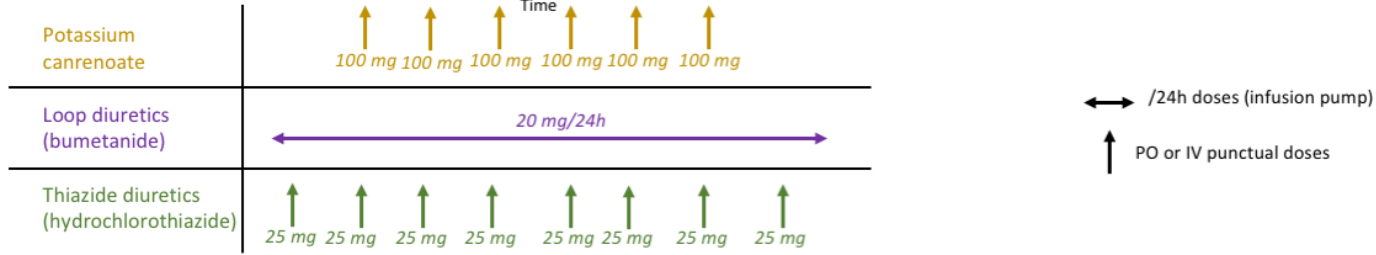
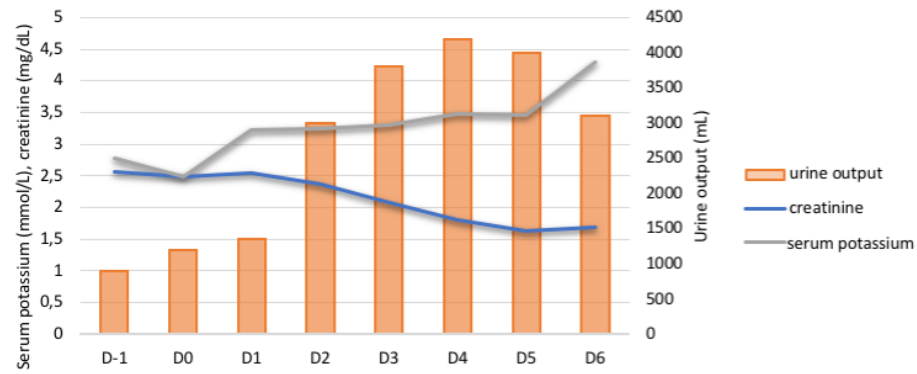
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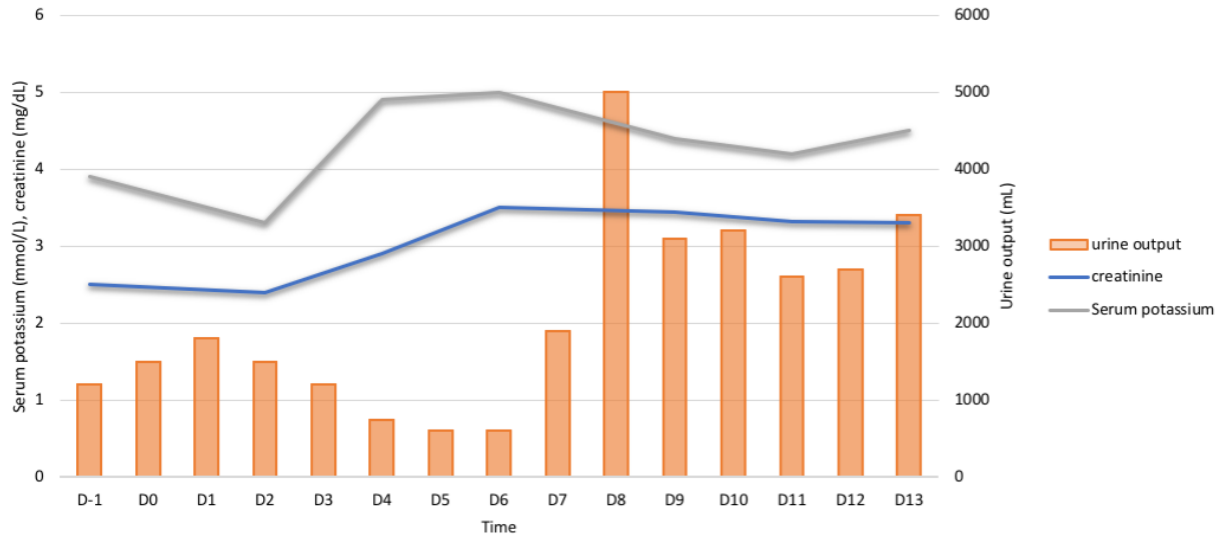
Figure 1: Urine output, creatinine and serum potassium levels before, during and after IV MRA treatment in 2 patients admitted for ADHF with diuretic resistance.



Second case



Third case



Weight (kgs)	76	75	74	75	75	76	73	71	67	65	65				
Blood Pressure (mmHg)	113/69	159/59	104/55	81/45	90/53	97/54	158/101	99/47	113/54	104/53	97/48	101/56	137/58	113/58	157/83
Estimated plasma volume	8.2	8.1		8.3			7.6		7.5		6.9				
Potassium Canrenoate (mg)		↑ 100	↑ 100 x2	↑ 100 x2	↑ 100 x2	↑ 100 x2	↑ 100 x2	↑ 100 x2	↑ 100 x2	↑ 100 x2	↑ 100 x2	↑ 100 x2	↑ 100 x2	↑ 100 x2	
Loop diuretics (bumetanide)	← 25 mg/24h →														
Thiazide diuretics (hydrochlorothiazide)	↑ 50 mg	↑ 50 mg	↑ 50 mg	↑ 50 mg	↑ 50 mg	↑ 50 mg	↑ 50 mg	↑ 50 mg	↑ 50 mg	↑ 50 mg	↑ 50 mg	↑ 50 mg	↑ 50 mg	↑ 50 mg	↑ 50 mg
Angiotensin II Receptor Blocker (Valsartan)		↑ 40 mg	↑ 40mg												

↔ /24h doses (infusion pump)
 ↑ PO or IV punctual doses