Intravenous Mineralocorticoid Receptor Antagonist Use in Acutely Decompensated Heart Failure with Diuretic Resistance

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Summary

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.

Case Reports

First case: an 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. IV 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 previous 24 hours. Within the next 24 hours, urine output increased from 400 to 2800 mL/day. Creatinine dropped from 30.5 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 A).

Second case: a 66-year-old man with hypertension, diabetes, chronic kidney disease, and 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. IV 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 previous 24 hours. Within the next 24 hours, urine output increased from 400 to 2800 mL/day. Creatinine dropped from 30.5 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 A).

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 was reported more than 40 years ago, but has long been 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 is 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.
Figure. Urine output, creatinine, and serum potassium levels before, during, and after IV MRA treatment in 3 patients admitted for ADHF with diuretic resistance.
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 B), and blood pressure (BP) was unchanged after canrenoate initiation.

**Third case:** an 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 Figure C. The patient was admitted after a weight increase of more than 10 kg. Despite the use of continuous infusion of bumetanide (25 mg/day) and hydrochlorothiazide (50 mg/day), diuresis remained less than 1.25 L/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 L/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 L/day. In the next few days, the patient achieved his normal dry weight (65 kg) 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 3 cases, creatinine noticeably improved while decongestion was achieved and serum potassium levels remained below 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 BP: indeed, canrenoate initiation did not have any significant impact on BP in all 3 cases.

As emphasized repeatedly, the fear of worsening renal function should not prevent one 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. 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 the 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 trial 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 a pharmacokinetic profile thus appears suboptimal in the setting of ADHF, and other approaches should be envisaged, such as IV 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 determined. In the first case, as a rapid and sizable 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.

**Conclusion**

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

**Disclosure**

**Conflicts of interest:** Pr. Rossignol reports grants and personal fees from AstraZeneca, Bayer, CVRx, Fresenius, and Novartis, personal fees from Grunenthal, Servier, Stealth Peptides, Vifor Fresenius Medical Care Renal Pharma, Idorsia, NovoNordisk, Ablative Solutions, G3P, Corvidia, and 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.
The other coauthors have no disclosures.

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