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Deposited on 23 March 2023

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Title: Serum bicarbonate and congestion: a potential biomarker for identifying and guiding management in diuretic resistance?

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Word count: 1257
This article refers to ‘Influence of Bicarbonate Levels on the Decongestive Response to Acetazolamide’ by P. Martens et al., on page X in this issue.

Diuretics have been used in the treatment of heart failure (HF) for over half a century, with loop diuretics being the principal treatment for relief of congestion in acute HF, with a class I indication from the European Society of Cardiology (ESC) guidelines for the treatment of HF. Despite this prominent role and being one of the most commonly prescribed medications for HF, there is significant variation in diuretic dosing and regimes. Prescribing practices within hospitals, and even departments, can vary, with diuretic use in decompensated HF often viewed as an ‘art’ and reliant on clinician experience. In many ways this is correct, given the wide variation in individual patient response to different diuretics and doses, however a recent consensus statement has suggested a standardised decongestive algorithm for use in HF. Historically there was not the same level of randomised controlled trial evidence to guide diuretic use that exists for other HF therapies. Until the Cardiorenal Rescue Study in Acute Decompensated Heart Failure (CARRESS-HF) trial, data supporting the use of combination diuretic regimes, or ‘sequential nephron inhibition’, a strategy often used in diuretic resistance, was limited to small randomised or non-randomised studies. However, over the past decade there have been a number of landmark randomised controlled trials of diuretic dosing and regimes which guide and inform the clinician. One of the most recent such trials is the Acetazolamide in Decompensated Heart failure with Volume OveRload (ADVOR) trial. This multicentre, randomised, placebo-controlled trial (n=519) reported that the addition of 500mg per day of acetazolamide to a standardised regime of intravenous loop diuretics led to a greater incidence of successful short-term decongestion, assessed using a composite outcome, in patients with acute decompensated HF.

In this post hoc exploratory analysis of the ADVOR trial, Martens et al. provide intriguing speculation into the potential role bicarbonate (HCO₃⁻) plays in the pathophysiology of congestion, and on the potential influence HCO₃⁻ has on the diuretic effect of acetazolamide when used in combination with intravenous loop diuretics.
diuretics. 9516 patients out of a possible 519 in the ADVOR trial were included in the analysis. High HCO₃, defined post hoc as baseline HCO₃ ≥ 27 mmol/L, was present in 45% of the population and associated with a higher diuretic dose use at baseline but not with a greater degree of congestion using the author’s congestion score or higher NT-proBNP. Acetazolamide, compared with placebo, resulted in a higher proportion of complete decongestion (primary endpoint), across all levels of baseline HCO₃ with the suggestion of a greater benefit of acetazolamide in patients with higher HCO₃ concentrations (interaction p = 0.065 (categorical) and 0.09 (continuous). Conversely, elevated HCO₃ at baseline was associated with a lower proportion of successful decongestion in patients in the placebo arm, and HCO₃ increased during treatment in the placebo arm (i.e., treatment with intravenous loop diuretic only). This is perhaps not surprising given the pharmacological effect of acetazolamide is to inhibit tubular bicarbonate resorption. The data presented by Martens and colleagues suggest that high levels of HCO₃ could identify patients who have or are likely to develop diuretic resistance, and in whom combination loop diuretics could be targeted, with acetazolamide potentially being the preferred additional diuretic agent when high HCO₃ is present. Conversely, higher HCO₃ could simply be a biomarker of higher diuretic dose use – the present analysis is unable to distinguish between these two hypotheses and would need to be tested prospectively.

The authors’ hypothesis that plasma HCO₃ is both influenced by diuretic therapy and also in turn influences the effectiveness of diuretic therapy in acute decompensated HF is supported by renal physiology, and the known increase in HCO₃ secondary to neurohormonal activation associated with loop diuretic use. 10 In CARRESS-HF, the largest trial of patients with diuretic resistance and HF, patients treated with combination high dose loop diuretic and high dose thiazide had an increase in blood HCO₃ from baseline to 96 hours compared to ultrafiltration (+3.3 mmol/L vs −0.9 mmol/L; p < 0.001). 3,10 Another randomised controlled trial of patients with diuretic resistance, the Comparison of Oral or Intravenous Thiazides vs Tolvaptan in Diuretic Resistant Decompensated Heart Failure (3T) trial, provides another useful comparison. 6 60 Patients were treated with high doses of loop diuretic and
randomised to a combination with either the thiazide-like diuretic metolazone, the thiazide diuretic chlorothiazide, or the vasopressin V2-receptor antagonist tolvaptan. HCO₃ levels increased from baseline to 48 hours by similar amounts seen in CARRESS-HF with treatment with metolazone (5±6 mmol/L), chlorothiazide (3±4 mmol/L), and tolvaptan (2±4 mmol/L).⁶ Levels of baseline HCO₃ in a pooled analysis of the DOSE-AHF, CARRESS-HF, ROSE-AHF trials (median 28 mmol/L) and in the 3T trial (mean 25 mmol/L) were comparable to those in ADVOR.¹⁰ It is unclear how many patients in ADVOR had diuretic resistance as only approximately a third of patients were on an intravenous diuretic prior to randomization, the median home maintenance furosemide equivalent dose of diuretic was 60mg daily, and patients were excluded if they were on high doses of loop diuretic, however given the comparable HCO₃ concentrations to other trials then we assume a proportion of patients had diuretic resistance.

No patients in the ADVOR trial were taking sodium–glucose co-transporter 2 inhibitors (SGLT2i). The authors highlight and acknowledge this limitation, and for important reasons did not include patients with this medication class. Both acetazolamide and SGLT2i act on the proximal tubule and preclinical studies have reported that SGLT2 inhibitors increase urinary bicarbonate excretion, an effect thought to be secondary to their effect on the Na⁺-H⁺ exchanger 3 (NHE3).¹¹ Not only have SGLT2i’s become one of the core disease modifying therapies across all ejection fractions in chronic HF, they have also been shown to be safe when initiated in the inpatient setting, and be effective in causing an increased diuresis and decongestion in this setting.¹²⁻¹⁵ In the randomized, double-blind, placebo-controlled, multicentre pilot study on the effects of empagliflozin on clinical outcomes in patients with acute decompensated heart failure (EMPA-RESPONSE-AHF) trial, total urine output at 24 hours was greater in patients randomised to empagliflozin 10mg (3442±1922 mL) compared with placebo (2400±993 mL) (P = 0.013).¹⁴ This cumulative urine output at 24 hours was similar to that reported in ADVOR (approximately 2500ml). Similar findings were seen in the Empagliflozin in Acute Decompensated Heart Failure (EMPAG-HF) trial, comparing empagliflozin 25mg to placebo in addition to standard HF therapy; empagliflozin with a 25% increase in urine output at 5 days (placebo-
corrected difference 2.2 L [95% CI, 8.4 to 3.6] , p 0.003). Although direct comparisons are not possible between these trials, these findings are intriguing given the proximity of action of both of these medications in the proximal convoluted tubule. The role of SGLT2i in the treatment of diuretic resistance is currently being tested in a multicentre randomised controlled clinical trial comparing dapagliflozin to metolazone (NCT04860011), which will inform the potential role of SGLT2i in diuretic resistance. A direct comparison between these two classes of medications in the setting of diuretic resistance will likely be required to address the question whether there is a synergistic effect of treatment with both acetazolamide and an SGLT2 inhibitor or whether the effect of acetazolamide is attenuated in patients taking an SGLT2 inhibitor. Whether serum HCO₃ concentrations can identify patients more likely to have benefit from combination therapy remains to be seen.

In summary, Mullens et al. present evidence suggesting that HCO₃ may have a role in identifying patients with congestion who may benefit from early combination diuretic therapy. Questions remain as to the treatment effect relationship between SGLT2 inhibitors and acetazolamide and should be a focus of future research.
Acknowledgements

None.

Funding Sources

None.

Disclosures

RTC reports he has received speakers’ honoraria from AstraZeneca, has served on an advisory board for Bayer AG and has received grant support from AstraZeneca (paid to his institution).

K.F.D. reports that his employer, the University of Glasgow, has been remunerated by AstraZeneca for work related to clinical trials. He has received speakers’ honoraria from AstraZeneca and Radcliffe Cardiology, has served on an advisory board for Us2.ai and Bayer AG, served on a clinical endpoint committee for Bayer AG, and has received grant support from Boehringer Ingelheim, Novartis and AstraZeneca (paid to his institution).

References


9. REFERENCE FOR HCO3 ADVOR manuscript


